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Acute recreational drug toxicity

Comparison of self-reports and results of immunoassay and additional analytical methods in a multicenter European case series

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Abstract

The aim of the study was to compare self-reported and analytically confirmed substance use in cases of acute recreational drug toxicity.

We performed a retrospective analysis of emergency department presentations of acute recreational drug toxicity over 2 years (October 2013 to September 2015) within the European Drug Emergencies Network Plus project.

Among the 10,956 cases of acute recreational drug toxicity during the study period, 831 could be included. Between the self-reported substance use and the toxicological results, the highest agreement was found for heroin (86.1%) and cocaine (74.1%), whereas inhalants, poppers, and magic mushrooms were self-reported but not analytically detected. Cathinones and other new psychoactive substances (NPS) could be detected using additional analytical methods. Among cases with both immunoassay (IA) and confirmation with mass spectrometry (MS), the results were consistent for methadone (100%) and cocaine (95.5%) and less consistent for amphetamines (81.8%). In cases with a positive IA for amphetamines (n = 54), MS confirmed the presence of 3,4-methylenedioxymethamphetamine (MDMA), amphetamine, methamphetamine, and NPS in 37, 20, 10, and 6 cases, respectively, also revealing use of more than 1 substance in some cases. MS yielded positive results in 21 cases with a negative IA for amphetamines, including amphetamine, MDMA, methamphetamine, and NPS, in 14, 7, 2, and 2 cases, respectively.

In conclusion, the highest agreement was found between self-reports and analytical findings for heroin and cocaine. The diagnosis of NPS use was mainly based on self-report. The IAs accurately identified methadone and cocaine, and MS had advantages for the detection of NPS and amphetamine derivatives.

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Abbreviations: 6-MAM = 6-monoacetylmorphine, CEDIA = cloned enzyme donor immunoassay, ED = emergency department, Euro-DEN = European Drug Emergencies Network, GC = gas chromatography, GHB = γ-hydroxybutyrate, IA = immunoassay, LC = liquid chromatography, LSD = lysergic acid diethylamide, MDMA = 3,4-methylenedioxymethamphetamine, MS = mass spectrometry, MS/MS = tandem mass spectrometry, NPS = new psychoactive substances, PCP = phencyclidine, SCRA = synthetic cannabinoid receptor agonist.

Keywords: acute recreational drug toxicity, chromatography, emergency department, immunoassay, mass spectrometry

1. Introduction

The recreational use of psychoactive substances is common. In the European Union, nearly 25% of the adult population has tried illicit drugs in their lives.[1] In addition to classic, established, recreational (illicit) drugs, many new psychoactive substances (NPS) have emerged worldwide in the last decade.[2]

In most cases of acute recreational drug toxicity presenting to the emergency department (ED), management is based on self-reported substance use and clinical presentation. However, relatively rapid analytical tests using immunoassays (IAs) can provide preliminary information about the substances that are used, especially if no other information is available by patient self-report. IAs use specific antibodies to qualitatively determine the presence of distinct drugs/drug classes.[3] Although relatively fast and easy to use, IAs have limitations because they can yield false-positives (e.g., cross reactivity with other compounds) or false-negatives (e.g., poor specificity or concentrations below the cut-off) and typically cannot detect NPS. Furthermore, the results are only qualitative (i.e., positive/negative) and a suspected positive result does not necessarily indicate acute intoxication. IAs are generally unspecific and more costly and time-consuming chromatographic methods (e.g., liquid chromatography [LC], gas chromatography [GC]) combined with mass spectrometry (MS) are needed for confirmation in case of a positive IA.[3] LC that uses very small particles in the stationary phase and a relatively high pressure in the mobile phase is referred to as high-performance LC. Tandem mass spectrometry (MS/MS) involves multiple steps of MS selection.[4] Such methods are often more sensitive and mostly more specific than IAs, but their costs, run time (e.g., the results might not be available the same day), and need for specialized personnel limit their use and benefits in the ED setting.

The present study compared self-reported and analytically detected substances in cases of acute recreational drug toxicity presenting to the ED. Our first objective was to investigate whether the analytical results that were obtained by IA and/or additional analytical methods provided additional information to the reports by the patients and proxies. We also investigated what substances were detected in patients with use of unknown agent (s) because knowing the substances used can influence the patients' management. Our second objective was to compare the IA results with the results from additional chromatographic-MS methods in cases in which both test results were available to identify possible advantages of using additional methods in cases of acute drug toxicity.

2. Materials and methods

The study was performed within the European Drug Emergencies Network (Euro-DEN) Plus project, the first year of which has been previously described in detail.[5,6] Briefly, using a minimum dataset of key demographic, predefined clinical, and outcome variables, the Euro-DEN Plus project collected information on ED presentations that had clinical features consistent with acute recreational drug/NPS toxicity from 16 sentinel centers in 10 European countries. Presentations associated with prescription or over-the-counter drugs were included if these drugs were used for recreational purposes but not if the presentation was related to self-harm or an adverse effect of a prescribed drug. Presentations related to lone alcohol toxicity, or not directly related to acute recreational drug toxicity (e.g., trauma and withdrawal), or associated with self-harm were excluded. The study was approved by the ethics committee of each participating center and performed in accordance with the Declaration of Helsinki.

Toxicological screening is not routinely being performed in all Euro-DEN Plus centers and is therefore available only in the minority of the cases; however, where it is undertaken as part of routine clinical care the results are recorded in the Euro-DEN Plus database. The present study included only cases with analytical confirmation. The retrospective analysis was performed using data collected during the first 2 years of the Euro-DEN Plus project (October 2013 to September 2015).

Data from the following centers were included: Basel, Drogheda, Dublin, London (2 centers), Mallorca, Oslo, and Paris. The following analytical tests were used: in Basel the Cloned Enzyme Donor-IAs (CEDIA, Thermo Fisher Scientific, Passau, Germany[7]), DRI IAs (Thermo Fisher Scientific[7]), an enzymatic assay (Bühlmann, Allschwil, Switzerland), and LC–MS/MS that covered over 770 substances, not including synthetic cannabinoid receptor agonists (SCRAs)[8] in some of the cases; in Drogheda, the CEDIA IA and enzyme multiplied IA technique; in Dublin, the Alere Drug Screen Urine Test Panel[9]; in London, the CEDIA IA (Thermo Fisher Scientific) and additional LC–MS/MS in some cases; in Mallorca, the DRI IA (Thermo Fisher Scientific) and GC–MS in some cases; in Oslo, ultra-high-performance LC–MS/MS; in Paris, IAs were performed using the ARCHITECT c4000 Clinical Chemistry, Abbott Core Laboratory,[10] LC–MS was performed rarely. More information about the analytical methods and most common samples used can be found as online supplement, http://links.lww.com/MD/C98.

The identification of cocaine metabolites using MS was categorized as positive identification of cocaine. Furthermore, for cases of self-reported heroin use, we categorized the detection of either 6-monoacetylmorphine (6-MAM) or morphine/opiates as a positive analytical result for heroin because heroin is rapidly deacetylated into 6-MAM (specific marker) and then further metabolized into morphine.

3. Results

During the 24-month data collection period, 10,956 cases that presented with acute recreational drug toxicity were reported to the Euro-DEN Plus project from the participating centers, with analytical confirmation available in 1674 cases (15.3%). Among these cases, 793 (47.4%) were excluded because in those centers

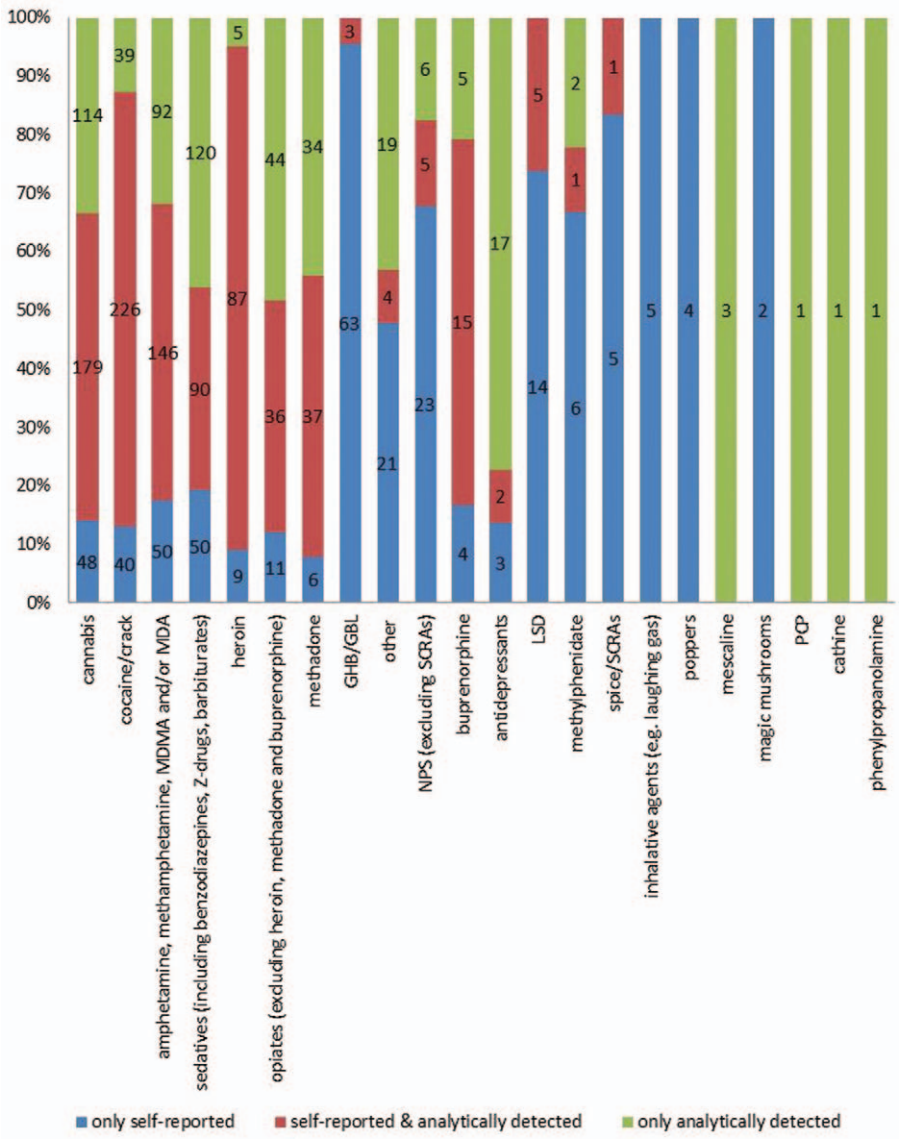

Figure 1. Substances (count of cases) self-reported and/or analytically detected in cases with at least 1 self-reported substance used (n = 768).

the self-reported substances were edited based on the analytical results. Of the remaining 881 cases, 50 were excluded because they only mentioned that an analytical test was performed but the results were not recorded. The remaining 831 cases were included in the present analysis—this represents 7.6% of all presentations and 49.6% of those in whom analytical testing was performed.

Among these 831 cases, at least 1 substance was self-reported in 768 cases. The substances that were self-reported compared with those that were identified analytically are shown in Fig. 1. The highest agreement between the self-reported substance use and the toxicological results was found for heroin (86.1%) and cocaine (74.1%), whereas inhalants, poppers, and magic mushrooms were self-reported but not analytically detected. NPS, excluding SCRAs, that were self-reported and/or analytically detected are shown in Table 1. In 1 case of self-reported use of synthetic cannabinoids, the SCRAs 5F-PB-22 and 5F-AKB48 were analytically confirmed using LC–MS/MS.

In 63 cases, no information was available from the patient (e.g., because of patient unconsciousness or uncooperativeness), or the agent that was used was unknown to the patient. The substances that were analytically detected in those cases are shown in Fig. 2.

In 213 of the 831 cases (25.6%), both IA and MS (LC–MS/MS or GC–MS) test results were available. Comparisons of the IA and MS results for the most commonly self-reported substances are shown in Table 2. There was relatively high agreement (overall percent agreement = positive IA and positive MS plus negative IA and negative MS/total) between the IA and the MS findings for methadone (100%), cocaine (95.5%), and heroin (91.7%), followed by opioids excluding methadone and heroin (85.7%), cannabis (84.4%), and benzodiazepines (84.2%), while the lowest agreement was seen for amphetamines (81.8%). See Table 2 for positive and negative percent agreement values for the IA compared with the MS.

Table 3 shows comparisons of the analytical results of both IAs and additional MS techniques in cases in which amphetamines were detected, including cases in which no use of these substances was self-reported (in contrast to Table 2 where only self-reported substances were considered). Using MS, identification of the

Table 1

Self-reported and/or analytically detected NPS (excluding SCRAs).

NPS	Self-reported (count of cases)	Analytically detected (count of cases)	Self-reported and analytically detected (count of cases)	Comment
2,5-Dimethoxy-4-bromophenethylamine (2C-B)	2			
25B-NBOMe[11]	3			
2,5-Dimethoxy-4-chloroamphetamine (DOC)	1			Same case with "Teenage mutant ninja turtle" and 2C-C
"Teenage mutant ninja turtle"	1			
2,5-Dimethoxy-4-chlorphenethylamine (2C-C)		1		
Paramethoxymethamphetamine (PMMA)	2			
Bromo-DragonFLY	1			
3-Methylmethcathinone (3-MMC)	1			
4-Methylethcathinone (4-MEC)	1			
3,4-Methylenedioxypyrovalerone (MDPV)		1		
α-PVP		2		
Mephedrone	8		3	
Methedrone	1			
Pentylone[12]		1		
Dimethyltryptamine (DMT)[13]	1			
"Devil bandit"	1			Toxicological analysis negative
"Charge white"	1			MDMA and fluorophenmetrazine detected
"Blue ghost"	1			Benzodiazepines and methamphetamine detected

α-PVP = α-pyrrolidinopentiophenone, MDMA = 3,4-methylenedioxymethamphetamine, NBOMe= N-2-methoxybenzyl-phenethlylamine; NPS = new psychoactive substances, SCRAs = synthetic cannabinoid receptor agonists.

exact substance(s) was possible in 51 of the 54 cases with a positive IA for amphetamines. Furthermore, amphetamine-type substances were detected by using MS in 21 cases with a negative IA, including the NPS pentylone and α-pyrrolidinopentiophenone.

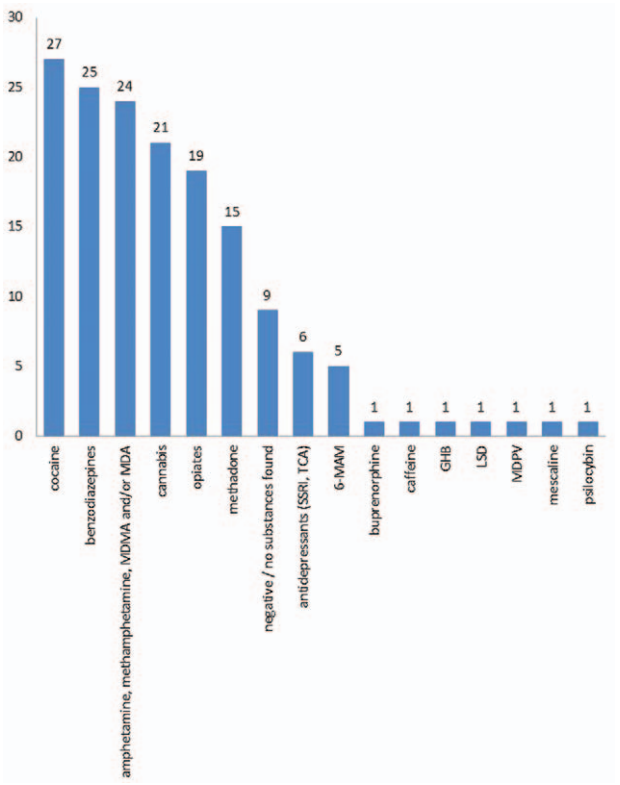

Figure 2. Substances (count of cases) analytically detected in cases with self-reported use of an unknown substance or with no information available (n = 63). SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressants.

4. Discussion

Toxicological analyses were performed only in a minority of the cases included in the Euro-DEN Plus project, which probably reflects normal practice in most European hospitals. The main finding of the present study was an agreement between self-reports of heroin and cocaine use and the analytical results in more than two-thirds of the cases. Laughing gas, poppers, magic mushrooms, γ-hydroxybutyrate (GHB), the GHB precursor γ-butyrolactone, NPS, lysergic acid diethylamide (LSD), and methylphenidate were mainly self-reported but not analytically detected. Mescaline, phencyclidine (PCP), cathine, and phenylpropanolamine were only analytically detected but not self-reported. In cases in which the substance was unknown by self-report, the most commonly analytically detected substances were cocaine, benzodiazepines, and amphetamine-type substances. Comparisons of the IA and MS results revealed high agreement for methadone and cocaine but lower agreement for amphetamines. Especially for the detection of amphetamine-type substances the MS detected amphetamines in cases in which the IA results were negative, and was able to identify the precise agents, including NPS, in cases of positive IA results. The probability to detect the self-reported substance was higher with the IA than MS for the detection of cannabis.

Knowledge of the pharmacological/toxicological properties of the substances is important for the interpretation of analytical results. For example, GHB was self-reported and analytically detected in only 4.5% of the cases, which is likely attributable to the very short plasma elimination half-life (20–50 min) that results in a small window of detection (≤4–5 h in blood and ≤12 h in urine).[14] In GHB cases, self- or proxy-reported use is the most important information for diagnosis (95.5% of the cases in our study). All NPS in the present study were detected only by additional analytical methods. If NPS use is not self-reported and if no MS method is used, then NPS use will remain undetected. Several recent studies on similar patient populations involving data from poison information centers have also demonstrated the importance of additional analytical methods in cases of NPS use, as self-reports have limitations, for example, people do not

Table 2

Comparison of the analytical results (both IA and MS [LC–MS/MS or GC–MS]) in cases of self-reported use.

		MS		
		Positive	**Negative**	**Total**
Cocaine (n = 66)				
IA	Positive	54	0	54
	Negative	3	9	12
	Total	57	9	66
Positive, negative, and total percent agreement between IA and MS		94.7%	100%	95.5%
Detected with IA	81.8%			
Detected with MS	86.4%			
Amphetamine, methamphetamine, or MDMA (n = 55)				
IA	Positive	34	2	36
	Negative	8	11	19
	Total	42	13	55
Positive, negative, and total percent agreement between IA and MS		81.0%	84.6%	81.8%
Detected with IA	65.5%			
Detected with MS	76.4%			
Cannabis (n = 32)				
IA	Positive	19	5	24
	Negative	0	8	8
	Total	19	13	32
Positive, negative, and total percent agreement between IA and MS		100%	61.5%	84.4%
Detected with IA	75%			
Detected with MS	59.4%			
Heroin (n = 24)				
IA	Positive	21	2	23
	Negative	0	1	1
	Total	21	3	24
Positive, negative, and total percent agreement between IA and MS		100%	33.3%	91.7%
Detected with IA	95.8%			
Detected with MS	87.5%			
Benzodiazepines (n = 19)				
IA	Positive	13	2	15
	Negative	1	3	4
	Total	14	5	19
Positive, negative, and total percent agreement between IA and MS		92.9%	60.0%	84.2%
Detected with IA	78.9%			
Detected with MS	73.7%			
Methadone (n = 9)				
IA	Positive	8	0	8
	Negative	0	1	1
	Total	8	1	9
Positive, negative, and total percent agreement between IA and MS		100%	100%	100%
Detected with IA	88.9%			
Detected with MS	88.9%			
Opioids, excluding heroin and methadone but including tramadol (n = 7)				
IA	Positive	4	1	5
	Negative	0	2	2
	Total	4	3	7
Positive, negative, and total percent agreement between IA and MS		100%	66.7%	85.7%
Detected with IA	71.4%			
Detected with MS	57.1%			

GC = gas chromatography, IA = immunoassay, LC = liquid chromatography, MDMA = 3,4-methylenedioxymethamphetamine, MS = mass spectrometry.

always know which substance they have ingested[15] and NPS names are often used incorrectly.[16] However, in some cases, even additional methods cannot detect all NPS (e.g., the LC–MS/MS method used in Basel was not designed to detect SCRAs). Furthermore, in cases in which IAs were used to test for a group of substances (e.g., opiates), certain limitations should be considered. For example, some synthetic opioids (e.g., tramadol) cannot be detected by IA tests for opiates, and Z-drugs (e.g., zolpidem, zopiclone) cannot be detected by IA tests for benzodiazepines.[3]

When interpreting analytical results, the possibility that some substances may be detected but not have clinical relevance should also be considered. Substances that are taken as comedications (e.g., antidepressants, methadone) or administered by paramedics (e.g., benzodiazepines) might be overrepresented in the analytical results. The same applies for substances with a long elimination half-life and substances that can be detected in samples beyond acute intoxication (e.g., cocaine metabolites can be found 24–48 h after use, cannabis is detectable in urine for days after a single high dose or weeks after heavier chronic

Table 3

Comparison of IA and MS (LC–MS/MS or GC–MS) results in cases with analytical detection of amphetamine-type substances.

		LC–MS/MS or GC–MS
IA positive for "amphetamines" (n = 54)	Lone MDMA	26
	Lone amphetamine	6
	Lone methamphetamine	1
	Amphetamine and MDMA	7
	Amphetamine and methamphetamine	4
	Methamphetamine and mephedrone	2
	MDMA and 2C-C	1
	Amphetamine and methamphetamine and MDMA	1
	Amphetamine and methamphetamine and mephedrone	1
	Amphetamine and MDMA and mephedrone	1
	Methamphetamine and MDMA and mephedrone	1
	Negative	3
IA negative for "amphetamines" (n = 21)	Lone amphetamine	10
	Lone MDMA	4
	Lone methamphetamine	1
	Lone pentylone	1
	Lone α-PVP	1
	Amphetamine and MDMA	3
	Amphetamine and methamphetamine	1

α-PVP = α-pyrrolidinopentiophenone, GC = gas chromatography, IA = immunoassay, LC = liquid chromatography, MDMA = 3,4-methylenedioxymethamphetamine, MS = mass spectrometry.

use[17]). Furthermore, substances used as cutting agents or added to enhance the action of the main substance (e.g., caffeine) can also be analytically detected without being self-reported or clinically relevant. Cross-reactivity (i.e., 1 limitation of IAs) can also lead to false-positives. Some examples of such cross-reactivity for some IAs include potential positive results for PCP or cannabis in the presence of lamotrigine, methamphetamine in the presence of ranitidine, and PCP in the presence of venlafaxine.[18] Cross-reactivity is a possible explanation for the 3 cases in the present study that tested positive for amphetamines with the IAs but negative with the additional technique.

Based on the present results, additional analytical methods appear to be superior to IAs with regard to the detection of amphetamines. However, for other substances, IAs appear to deliver accurate results, with nearly 100% agreement with the MS for substances such as methadone and cocaine. Possible explanations for the positive IA results in some cases and negative MS results may be associated with cross-reactivity or, in the case of cannabis, limitations of the additional technique that is used (e.g., cannabis can sometimes stick to the tubes, leading to false-negatives).

The present study has limitations. First, the study was retrospective and included multiple centers and the toxicological tests were not performed using the same methods in all of the centers. Reporting and analytical biases cannot be excluded in some cases as we used self-reports as references, which have a varying degree of accuracy, and substances that were not reported and could not be detected with the method(s) used would go undetected. Furthermore, some of the substances detected could be false positives or part of the patient's medication. We also did not derive sensitivity values from testing against gold standards of controlled drug administration but rather tried to reflect the likelihood of detecting a substance that was reportedly used. For the calculation of sensitivity values, confirmatory analytical results obtained by LC–MS/MS methods or similar should be considered the gold standard, and not IA or self-reports. In order to overcome most of those limitations a prospective study design using a high-quality test as the gold standard (e.g., LC–MS/MS) would be needed.

5. Conclusion

In conclusion, the present study found high agreement between self-reported and analytically detected cocaine and heroin use. Inhalants, poppers, magic mushrooms, GHB, LSD, NPS, and methylphenidate were mainly self-reported but not analytically detected. The IAs accurately detected methadone, cocaine, and heroin. The MS methods presented advantages in detecting NPS and differentiating amphetamine-type substances. Although toxicological screening tests are not routinely used in most hospitals across Europe, our findings suggest that they can be helpful, mostly in cases of use of unknown agents and unclear clinical presentations, provided that the results are interpreted correctly.

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References

[1] European Monitoring Centre for Drugs and Drug AddictionEuropean Drug Report 2016: Trends and developments. 2016;European Monitoring Center for Drugs and Drug Addiction, Lisbon:Available at: http://www.emcdda.europa.eu/edr2016.
[2] Hill SL, Thomas SH. Clinical toxicology of newer recreational drugs. Clin Toxicol (Phila) 2011;49:705–19.
[3] Alere. Triage TOX Drug Screen Product Insert: Rapid Qualitative Simultaneous Detection of Drug and/or the Major Urinary Metabolites of 10 Different Drug Classes (11 Unique Assays). San Diego, CA: Alere; 2013. Available at: http://www.sabes.it/download/kh/bozen/TRIAGE_-_metodica.pdf.
[4] McNaught AD, Wilkinson A. IUPAC Compendium of Chemical Terminology: The Gold Book, version 2.3.3. (2014). Research Triangle Park: International Union of Pure and Applied Chemistry; 1997. Available at: http://goldbook.iupac.org.
[5] Dines AM, Wood DM, Yates C, et al. Acute recreational drug and new psychoactive substance toxicity in Europe: 12 months data collection from the European Drug Emergencies Network (Euro-DEN). Clin Toxicol (Phila) 2015;53:893–900.
[6] Wood DM, Heyerdahl F, Yates CB, et al. The European Drug Emergencies Network (Euro-DEN). Clin Toxicol (Phila) 2014;52:239–41.
[7] Thermo Scientific. CEDIA, DRI and QMS Technologies. Fremont: Thermo Scientific; 2012. Available at: https://tools.thermofisher.com/content/sfs/brochures/10017521MTL_Technology%20Brochure%20NS.pdf.
[8] Mueller DM, Rentsch KM. Online extraction toxicological MS(n) screening system for serum and heparinized plasma and comparison of screening results between plasma and urine in the context of clinical data. J Chromatogr B Analyt Technol Biomed Life Sci 2012;883–884:189–97.
[9] Alere. Drug Screen Urine Test Panel. San Diego, CA: Alere; 2015. Available at: http://www.aleretoxicology.co.uk/en/home/products-services/drug-testing/products/urine-drug-screen-test-panel.html.
[10] Abbott. Architect c4000. Baar: Abbott. Available at: https://www.corelaboratory.abbott/int/en/offerings/brands/architect/architect-c4000.
[11] Rickli A, Luethi D, Reinisch J, et al. Receptor interaction profiles of novel N-2-methoxybenzyl (NBOMe) derivatives of 2,5-dimethoxy-substituted phenethylamines (2C drugs). Neuropharmacology 2015;99:546–53.
[12] Simmler LD, Rickli A, Hoener MC, et al. Monoamine transporter and receptor interaction profiles of a new series of designer cathinones. Neuropharmacology 2014;79:152–60.

[13] Rickli A, Moning OD, Hoener MC, et al. Receptor interaction profiles of novel psychoactive tryptamines compared with classic hallucinogens. Eur Neuropsychopharmacol 2016;26:1327–37.
[14] Schröck A, Hari Y, König S, et al. Pharmacokinetics of GHB and detection window in serum and urine after single uptake of a low dose of GBL: an experiment with two volunteers. Drug Test Anal 2014;6:363–6.
[15] Helander A, Bäckberg M. New psychoactive substances (NPS)—the Hydra monster of recreational drugs. Clin Toxicol (Phila) 2017;55:1–3.
[16] Bäckberg M, Tworek L, Beck O, et al. Analytically confirmed intoxications involving MDMB-CHMICA from the STRIDA Project. J Med Toxicol 2017;13:52–60.
[17] Buchan BJ, Dennis ML, Tims FM, et al. Cannabis use: consistency and validity of self-report, on-site urine testing and laboratory testing. Addiction 2002;97(suppl 1):98–108.
[18] Alere. Cross-Reaction Guide: For Use With Alere Urine Drug Screening Devices. San Diego, CA: Alere; 2013. Available at: https://www.transmedco.com/mm5/media/Cross_Reaction_Guide.pdf.