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New psychoactive substances as adulterants of controlled drugs. A worrying phenomenon?

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The use of new psychoactive substances (NPS) as adulterants has received little attention in the literature. In this paper, results from Energy Control's drug checking service documenting the use of NPS as adulterants of controlled drugs are presented, and some reflections about possible explanations for this new phenomenon, potential risks for users, and challenges that it poses are discussed. From 2009 to 2012, 24 NPS belonging to several chemical classes such as phenethylamines, substituted cathinones, tryptamines, and methoxetamine were identified in 173 samples believed to be MDMA, amphetamine, ketamine, cocaine, mescaline, or methamphetamine. The NPS adulterant most frequently observed was 2-(4-bromo-2,5-dimethoxyphenyl) ethanamine (2C-B) followed by 1-(4-fluorophenyl)propan-2-amine (4-FA). Sixty-nine different combinations of substances were detected: 20 involving a controlled drug combined with an NPS, and 49 involving one or more NPS that substituted the controlled drug. As these combinations could pose substantial risks to users, the need to improve knowledge about toxicity associated with these combinations, and the danger of these substances being incorporated into the products of illegal markets, are highlighted. Drug checking services and the European Union's early-warning system operated by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and Europol can play an important role in reducing the harm associated with this phenomenon.

Keywords: new psychoactive substances; adulteration; controlled drugs; illegal market

Introduction

Research has mainly focused on the identification and characterization of new psychoactive substances (NPS) whilst there are scarce data about the presence of these drugs on the illegal market replacing other substances. In Spain, Energy Control, a harm reduction project of the non-governmental organization Asociación Bienestar y Desarrollo, has carried out drug checking services since 1998 (also known as drug testing services or, in the past, pill testing services) as a harm reduction strategy with more than 12 000 substance samples analyzed. Approximately 1000 of the samples were purchased as NPS. Drug users can bring their drugs to a central facility or give them to Energy Control's staff at festivals, clubs, and underground raves where the project provides outreach activities. Drugs are tested through a combination of validated analysis techniques (thin layer chromatography at Energy Control's facilities, and gas chromatography associated with mass spectrometry at the Institut de Recerca Hospital del Mar - IMIM in Barcelona), and results are personally comunicated to users along with harm reduction advice. A more detailed description of analytical procedures is available in a previously published paper.[1] Although most samples received were purchased by drug users as 3,4-methylenedioxymethamphetamine (MDMA), amphetamine, and cocaine, the number of different substances, including NPS, has increased over the years. In addition, the service permits the monitoring of adulteration, as it poses substantial risks to users.[2–8]When adulteration or other relevant issues (e.g. excessive amounts of the drug in certains batches or samples) are identified, several mechanisms are implemented in order to communicate this information to the drug users: publications on websites, forums and social networks, and posters in recreational settings where the project provides outreach activities. The Spanish Observatory on Drugs and the European early-warning system on NPS are also informed when NPS are involved.

Adulteration of controlled drugs is quite common.[9–15] A broad variety of substances are used to mimic the effects of controlled drugs (e.g. local anaesthetics in cocaine or caffeine in amphetamines) and to increase profits for sellers. Adulteration can be done in two different ways: either a substance (psychoactive or not) is added to a controlled drug or, simply, the controlled drug is replaced with another psychoactive substance. At the same time, NPS are being increasingly sold on 'legal high' or 'research chemical' markets. Since 2009 these novel drugs have also been found as adulterants of controlled drugs in our drug checking service. The first time they were identified as adulterants coincided with a shortage of MDMA observed in several European countries.[16,17] That year, 2-(4-bromo-2,5-dimethoxyphenyl)ethanamine (2C-B) began to be sold as MDMA in Spanish recreational settings.[1] In other European countries, other substances (e.g. 2-methylamino-1-(4-methylphenyl)propan-1-one or mephedrone) were also marketed as substitutes for MDMA.[14]

In this perspective paper, the presence of NPS as adulterants of controlled drugs is documented, and some reflections about possible explanations for this new phenomenon, potential risks for users, and challenges that it poses are discussed. It is worth mentioning that, in this paper, 2C-X compounds are considered as NPS since they are taken to be as such by the Spanish Observatory on Drugs.[18] On the other hand, ketamine is not considered here as an NPS because, although it is not under

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international control, it has been present for a number of years on the Spanish drug market.[19]

What have we found?

From 2009 to 2012, NPS were identified in 173 samples of controlled drugs submitted to our Drug Checking Service. In 2009, NPS as adulterants were found in samples submitted as MDMA, amphetamine, and mescaline. Since then, however, there has been a growth in the number of controlled drugs adulterated with NPS (Table 1).

As can be observed, MDMA was the substance in which the greatest number of samples adulterated with NPS was observed, especially in tablets, followed by amphetamine.

A total of 24 NPS were detected as adulterants of controlled drugs (Table 2). They belonged to several chemical classes such as phenethylamines (1-phenylethylamine, 25C-NBOMe, 25I-NBOMe, 2C-B, 2C-C, 2C-E, 2C-I, 2-FA, 3,5-DMA, 3-FA, 4-FA, 4-FMA, DMA, DOC, DOI), substituted cathinones (2-MMC, 4-MEC, buphedrone, butylone, dimethylcathinone, mephedrone, methylone), tryptamines (4-acetoxy-DIPT), and methoxetamine. 2C-B was the most frequently observed NPS adulterant, especially in MDMA tablets, followed by 4-FA in amphetamine. Substituted cathinones, such as mephedrone or methylone, were also reported as adulterants of MDMA, especially in crystal format. Since 2011, methoxetamine has been noticeably found in ketamine samples.

Table 3 presents the sum of the combinations of substances detected in the samples. As can be observed, 69 different combinations were found in all 170 samples: 49 different compositions involved one or more NPS, while 20 involved a controlled drug combined with NPS (highlighted in italics in Table 3). When mixtures were detected, the main constituent is highlighted in bold font in Table 3.

What are the implications of these findings?

Whilst it is apparent that a market for NPS has been established in several regions around the world, the arrival of these compounds onto the illegal market to replace other substances is a phenomenon that must be followed with attention. If knowledge about the risks associated with the use of NPS is still limited, even less information is available on the combination of several NPS in a single product or the combination of one or more NPS with other drugs such as MDMA, cocaine, amphetamine, or LSD. The scarcity of data concerning active and toxic doses for many of these compounds, and the lack of information about potential interactions between these substances, present two major uncertainties with respect to the risks associated with the use of NPS. These issues are particularly important given that drug users may be exposed to risks that, if known, they might want to avoid.

Adulteration of controlled drugs is a matter of consumer fraud. It seeks to reduce the amount of the drug in question by adding other compounds, psychoactive or not.[15] When these compounds are psychoactive, they attempt to mimic some of the expected effects of the substance, as in the case of local anaesthetics in cocaine or caffeine in amphetamines. The diversion of NPS onto the illegal market in order to be used as adulterants (they are not sold as 'drugs' on this market) could be explained by the fact that, for many sellers (specially small-scale ones) NPS are more readily available than 'classic' adulterants such as mCPP, phenacetin, levamisole, or local anaesthetics.[14] On the other hand, at least in Spain, the use of non-controlled NPS as adulterants involves fewer legal risks which could be an incentive for sellers since they cannot be criminally charged. Such speculations will need to be addressed in the forthcoming years as the use of NPS as adulterants may prove to be more than a local phenomenon. The use of several NPS as adulterants of MDMA has also been documented by other drug checking services in Switzerland, Austria, and the United States.[20,21] For example, in 2012, methylone was identified in 1.65% of MDMA tablets analyzed by a drug checking service in Switzerland;[22] and methylone, 4-MEC, and mephedrone were identified in 8.84%, 10.2%, and 9.52%, respectively, of MDMA tablets analyzed by the drug checking service 'Checkit!' in Austria.[20,23,24]

The arrival of NPS on the illegal market could result in their incorporation into the products of this market as has been the case for 2C-B in Spain, a drug that went from being sold as MDMA in 2008 to having its own 'market share'.[1] The same might be happening again in Spain with methoxetamine[20,25] whose effects are similar to those of ketamine but with slower onset and longer duration of action.[26] However, as in the case for 4-FA mixed with amphetamine, it is difficult to ascertain the real purpose of using these substances as adulterants.

Poor synthesis can be identified by the presence of by-products in samples. Similar findings have been documented previously.[27] This increases the uncertainty related to associated risks since the effects of most of these compounds on health remain unknown. Nevertheless, in some specific cases, some severe damage has begun to be documented.[28]

The results presented in this perspective paper raise a number of challenges. To date, most research has focused on individual substances without considering that on the market they are sometimes combined with each other and, as described here,

Table 1. Number of illegal drug samples submitted to Energy Control's drug checking services in which NPS were detected

Sample submitted as	Year				Total
	2009	2010	2011	2012	
MDMA (tablets)	47	8	16	16	87 (50.3%)
MDMA (crystal)	11	12	2	4	29 (16.8%)
Amphetamine	6	4	6	6	22 (12.7%)
Ketamine	-	-	4	12	16 (9.2%)
LSD	-	-	2	7	9 (5.2%)
Cocaine	-	1	-	3	4 (2.3%)
Methamphetamine	-	-	4	-	4 (2.3%)
Mescaline	2	-	-	-	2 (1.2%)

Table 2. Presence of NPS in illegal drugs submitted to Energy Control's drug checking service

	MDMA Pill	MDMA Crystal	Amph.	Ketamine	LSD	Cocaine	Methamph	Mescaline	Total
1-Phenylethan-1-amine		5							5
25C-NBOMe[a]					1				1
25I-NBOMe[b]					3				3
2C-B[c]	71				3			1	75
2C-C[d]					1				1
2C-E[e]					1				1
2C-I[f]	3	1				1			5
2-FA[g]	1								1
2-MMC[h]	1								1
3,5-DMA[i]			1						1
3-FA[j]	2						4		6
4-ACO-DIPT[k]					1				1
4-FMA[l]	1								1
4-FA[m]			20						20
4-MEC[n]		1		1					2
Buphedrone[o]	1	1				1			3
Butylone[p]						1			1
Dimethylcathinone[q]	1								1
DMA[r]					1				1
DOC[s]					1				1
DOI[t]								1	1
Mephedrone[u]	4	8	1	4					17
Methylone[v]	1	13							14
Methoxetamine[w]	1		1	15		1			18
Nº of different NPS	11	6	4	3	8	4	1	2	

[a]2-(4-chloro-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine,
[b]2-(4-iodo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine,
[c]2-(4-bromo-2,5-dimethoxyphenyl)ethanamine,
[d]1-(4-chloro-2,5-dimethoxyphenyl)-2-aminoethane 1-(4-chloro-2,5-dimethoxyphenyl)-2-ethanamine,
[e]1-(2,5-dimethoxy-4-ethylphenyl)-2-aminoethane,
[f]2,5-dimethoxy-4-iodophenethylamine,
[g]1-(2-fluorophenyl)propan-2-amine,
[h]2-(methylamino)-1-(2-methylphenyl)propan-1-one,
[i]2-(3,5-dimethoxy-phenyl)-1-methyl-ethylamine,
[j]1-(3-fluorophenyl)propan-2-amine,
[k]3-[2-[bis(1-methylethyl)amino]ethyl]-1H-Indol-4-ol acetate,
[l]1-(4-fluorophenyl)-N-methylpropan-2-amine,
[m](RS)-1-(4-fluorophenyl)propan-2-amine,
[n]2-ethylamino-1-(4-methylphenyl)propan-1-one,
[o]2-(methylamino)-1-phenylbutan-1-one,
[p]1-(1,3-benzodioxol-5-yl)-2-(methylamino)butan-1-one,
[q]2-dimethylamino-1-phenylpropan-1-one,
[r]2-(3,4-dimethoxyphenyl)propylamine,
[s]1-(4-chloro-2,5-dimethoxy-phenyl)propan-2-amine,
[t]1-(2,5-dimethoxy-4-iodophenyl)-propan-2-amine,
[u]2-methylamino-1-(4-methylphenyl)propan-1-one,
[v](±)-2-methylamino-1-(3,4-methylenedioxyphenyl)propan-1-one,
[w]2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone

with other controlled substances. For this reason, research should also be directed towards the study of the toxicity associated with the interaction of these compounds as they could be responsible for emergency room admissions.[29–33] The aim should be to provide this knowledge not only to health professionals, but also to drug users themselves in order either to discourage the use of these combinations or to offer them harm reduction advice. One of the biggest challenges is to transmit this information to users without advertising NPS. For this reason, when Energy Control communicates the test results of controlled drugs adulterated with NPS to drug users, NPS are always treated as adulterants with unknown risks and, therefore, their consumption should always be avoided.

Due to the fact that this work was carried out with samples given voluntarily by drug users, it is not possible to determine the degree of penetration of this type of adulteration in the

Table 3. Different compositions found in samples adulterated with NPS

Sample submitted as	Composition[a,b]	n
MDMA tablets	2-FA	1
	2-MMC + caffeine + hexadecanoic acid + octadecanoic acid	1
	2C-B	67
	2C-B + *ketamine*	2
	2C-B + **mephedrone**	1
	2C-B + **caffeine** + mephedrone	1
	2C-I	3
	3-FA	2
	4-FMA	1
	1-(4-Fluorophenyl)piperazine (pFPP) + buphedrone + **caffeine** + unknown	1
	1-(4-Methoxyphenyl)propan-2-amine (PMA) + **caffeine** + dimethylcathinone + pFPP + synthesis by-products + unknown	1
	1-[3-(Trifluoromethyl)phenyl]piperazine (TFMPP) + **ephedrine** + caffeine	2
	MDMA* + *methoxetamine	1
	Mephedrone	2
	Methylone	1
	Total of different combinations	15
MDMA crystal	1-Phenylethan-1-amine	5
	2C-I	1
	4-MEC + synthesis by-products	1
	Buphedrone	1
	1,4-Dibenzylpiperazine (DBZP) + ***MDMA*** + *methylone*	1
	MDMA + *mephedrone*	1
	MDMA + *mephedrone* + *synthesis byproducts*	1
	Mephedrone	5
	Mephedrone + synthesis by-products	1
	Methylone	11
	Methylone + synthesis by-products	1
	Total of different combinations	11
Amphetamine	4-FA	1
	4-FA + **caffeine**	3
	4-FA + **caffeine** + *N,N*-di-(β-phenylisopropyl)amine (DPIA)	2
	4-FA + synthesis by-products	2
	3,5-DMA + *4-FA* + *amphetamine* + ***caffeine***	1
	4-FA + *amphetamine*	3
	4-FA + *amphetamine* + ***caffeine***	3
	4-FA + *amphetamine* + *unknown* + *unknown*	1
	4-FA + *amphetamine* + *DPIA*	1
	Amphetamine + *4-FA* + *DPIA* + ***caffeine***	1
	4-FA + *amphetamine* + *synthesis byproducts*	1
	4-FA + *acetylated 4-FA* + *MDMA*	1
	Mephedrone	1
	Methoxetamine	1
	Total of different combinations	14
Ketamine	4-MEC	1
	Caffeine + *ketamine* + ***methoxetamine***	1
	Caffeine + *MDMA* + *mephedrone* + ***methoxetamine*** + *unknown*	1
	Azosemide + *ephedrine* + ***ketamine*** + *mephedrone* + *methoxetamine*	1
	Ketamine + ***methoxetamine*** + *synthesis by-products*	1
	Mephedrone + **methoxetamine** + synthesis by-products + unknown	1
	Mephedrone + **methoxetamine** + unknown + unknown	1
	Methoxetamine	3
	Methoxetamine + benzoic acid	1
	Methoxetamine + caffeine	3
	Methoxetamine + caffeine + unknown	1
	Methoxetamine + synthesis by-products	1
	Total of different combinations	12
LSD	**25C-NBOMe** + 2C-C	1

(Continues)

Table 3. Continued

Sample submitted as	Composition[a,b]	n
	25I-NBOMe	1
	25I-NBOMe + 2-methoxy phenylacetone	1
	25I-NBOMe + 2-methoxy phenylacetone + 4-acetoxy-DIPT	1
	2C-B	1
	2C-B + hexadecanoic acid + unknown	1
	2C-E + synthesis by-products	1
	DOC + DMA + octadecanoic acid + unknown + unknown	1
	2C-B + *LSD* + *synthesis by-products*	1
	Total of different combinations	9
Cocaine	2C-I	1
	Buphedrone	1
	Cocaine + ***butylone*** + ***cinnamoylcocaine***	1
	Cocaine + *caffeine* + *methoxetamine* + *levamisole* + *paracetamol* + *phenacetin* + *procaine*	1
	Total of different combinations	4
Methamphetamine	3-FA	2
	3-FA + unknown	2
	Total of different combinations	2
Mescaline	2C-B	1
	DOI	1
	Total of different combinations	2

[a] The main constituent is highlighted in bold font

[b] Compositions involving an illicit drug combined with one or more NPS are highlighted in italics

illegal market in Spain. However, drug checking services are very close to drug users, analyze large numbers of samples, and have the ability to respond quickly to emerging trends in drug use settings. In this sense, communication is carried out through several channels that ensure we effectively reach drug users (e.g. websites, social networks, outreach activities) in a short period of time, usually less than a week.[34] Therefore, these services and the EU's early-warning system can play an important role in reducing the harm associated with this phenomenon.

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