TWO YEARS OF NPS IN ITALY: A SNAPSHOT OF DRUGS CONFISCATED IN THE PERIOD 2013-2015

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ABSTRACT

The diffusion of NPS in the illicit drug market is a problem worldwide. The aim of the study is to report the analytical approach used for the identification of NPS in unknown seizures and to describe our analytical experience on some of the NPS confiscated in the Italian territory in the last two years.

In the period 2013-2015 we analyzed 162 seizures of substances purchased through the internet by Arma dei Carabinieri. 35 seizures (22%) were crystals of 3-methylmetcathinone (3-MMC). This substance is controlled in Italy, but not in other Countries such as the Nederland, from which the shipments originated. 33 seizures (20%) were crystals of 4-methylethcathinone (4-MEC), 19 confiscations (12%) were powders containing methylenedioxypyrovalerone (MDPV). N,N-diallyl-5-methoxytryptamine (5-MeO-DALT) was identified in 5 powders, ethylphenidate in six powders, pyrrolidinophenones in fourteen seized powders: 6 α-PVP (alpha-pirrolidinovalerophenone), 6 α-PHP (alpha-pyrrolidinohexaphenone) and 2 α-PVT (α-pyrrolidinopentiothiophenone). Other substances identified were cathinones such as pentedrone, methylone, buthylone, ethylone, methedrone, clephedrone, dimethylmethcathinone DMMC, flephedrone, MPPP (4-methyl-alpha-pyrrolidinopropiophenone), bk-2C-B (2-amino-1-(4-bromo-2,5-dimethoxyphenyl)ethan-1-one). Substances from other classes were diphenidine, encountered for the first time in Europe, NM2AI (N-methyl-2aminoindane), MPA (1-(thiophen-2-yl)-2-methylaminopropane), MTTA (mephtetramine), 4-APB and 6-APB (4-(2-aminopropyl)benzofuran and 6-(2-aminopropyl)benzofuran), 2-fluoromethamphetamine, 1mCPP (1-meta-chlorophenylpiperazine). Only three seizures contained synthetic cannabinoids, and were herbal material soaked with N-(1-adamantyl)-1-pentyl-1H-indazole-3-carboxamide (AKB 48), or with a mixture of 5-fluoro-AKB and BB-22 (1-(cyclohexylmethyl)-8-quinolinyl ester-1H-indole-3-carboxylic acid). In some cases there were mixtures of drugs, such as granules containing 4-MEC and pentedrone, in one case with traces of diphenidine. In other cases 5-MeO-DALT, ethylphenidate and caffeine were mixed together. In one case the mixture was flephedrone and methoxethamine. In one case the sample contained methylone, ethylone, methedrone, 4-fluoroamphetamine, 5-MeO-DALT and 5MeO-MIPT. Six shipments from Philippines contained crystals of pure methamphetamine. 9 seizures were tablets containing sildenafil. The proposed analytical approach allowed the identification of NPS in seizures, also in absence of an analytical standard. The analyses performed showed the presence in the Italian territory of a wide number of NPS coming from other Countries. Our study confirms the threat for public health, especially when mixture of NPS are sold and when it is not reported the real content of the shipment.

Key-words: forensic toxicology, NPS, confiscated material, HRMS, GC-MS

INTRODUCTION

The diffusion of NPSs in the illicit drug market is a problem worldwide. According to the UNODC "2014 Global Synthetic Drugs Assessment", 348 NPSs were identified for the first time between 2008 and 2013, 97 only in 2013 [1]. The phenomenon is becoming more and more serious, as in 2014 101 new psychoactive substances were reported for the first time to the EU Early Warning System [2].

The heterogeneous chemical structures of NPSs allow them to be classified in several chemical classes, including synthetic cannabinoids, synthetic cathinones, ketamines and phencyclidine-type substances, phenethylamines, piperazines, benzofurans, aminoindanes, tryptamines, substances not pertaining to any of these, and plant-based substances. The distribution and the prevalence of these substances vary across the different geographical areas and of course over time [3].

These substances are often designed to be structural analogue of a "traditional" drug or controlled substance in order to have a similar effect and in the meanwhile avoid the law. For example methoxetamine is an analogue of ketamine (the 2-chloro group on the phenyl ring is replaced with 3-methoxy group and the N-methyl group is replaced with N-ethyl group).

Currently legal status of NPSs varies in each country, even within the European Union. In Italy since 2010 various decrees were issued to update the list of controlled psychotropic substances, where the chemical substances are not simply cited name by name, but also as groups of structurally related analogues such as the compounds derived from 3-phenyl acetylindole, the structures analogue to 3-(1-naphtoyl)indole, 3-benzoylindole and the ones derived from 2-amino-1-phenyl-1-propanone [4].

For the laboratories involved in the analysis of drugs, the identification of new substances could be very challenging because their number is continually growing and consequently there is the possibility of a lack of reference standards and analytical data from scientific literature at the beginning of their distribution in a specific area. In these cases a special approach involving the combination of several analytical techniques is required for their correct identification. Another critical issue, besides their identification, is that these substances are under control of the law only in some Countries, depending by the specific National regulations.

The aim of this study is to show how the application of the analytical approach developed for the analysis of NPSs in unknown seizures [5, 6] allowed successful identification of NPS in 162 confiscations in the Italian territory in the last two years, with special attention to their inclusion or not in the list of substances controlled by the law in Italy.

EXPERIMENTAL

GC-MS

The GC-MS system used was an Agilent 7890 gas chromatograph, coupled to an Agilent 5975c quadrupole mass detector (Agilent Technologies Italia, Milan, Italy) operating at 70 eV in

electron ionisation mode. The mass detector was operated in scan mode (scan range from m/z 50 to 600).

LC-HRMS

The LC-HRMS system was composed of a Thermo ULTIMATE 3000 system equipped with an analytical column Thermo Acclaim RSLC 120 C18 (2.1 x 100 mm, 2.2 µm particle size), coupled to a Thermo single-stage Orbitrap (Exactive) MS system, interfaced with a HESI Ion Max source. Data were acquired in full scan mode over a mass range of 100-600 m/z. The instrument operated in positive ion mode with a resolving power of 100.000 FWHM. A further set of experiments was performed with in-source collision-induced dissociation (CID) at different voltage settings (20V, 30V, and 40V), acquiring ions from 50 to 450 m/z to obtain the accurate masses of both precursor and fragment ions at a resolving power of 50.000 FWHM.

NMR analyses

^{1}H NMR spectra were obtained on a Varian Mercury 300 spectrometer using $CDCl_3$ (diphenidine hydrochloride,), DMSO-d6 /CDCl3 = 9/1 for bk-2CB or $CDCl_3/CD_3OD$ = 8/2 (6-APB, 3-MMC, fluoromethcathinone, 3-CMC and 2F-methamphetamine and 3-chlorophenylpiperazine) as solvent and TMS as internal standard.

Analytical approach

The analytical approach we used for the identification of unknown NPS along with sample preparation procedures and detailed instrumental conditions are described in detail elsewhere [5, 6].

Briefly, all the samples were analysed firstly using GC/MS, in some cases after specific derivatisation, then by LC/HRMS with and without fragmentation to study the accurate mass of the molecule and of its characteristic fragments, and, when the discrimination of isomers was needed, also by NMR.

RESULTS

162 samples were analyzed between September 2013 and June 2015. In most cases (94%) the samples contained only one active compound. For the remaining 6%, two, three or even seven different substances were identified in the same sample, and often these mixture contained cathinones.

NPS identified, shematized in figure 1, are described below, grouped in three major classes: cathinones, synthetic cannabinoids and miscellanea. Their structures are shown in figures 2 and 3. Figure 2 shows the substances scheduled as controlled drugs in Italy (their 2-amino-1-phenyl-1-propanone moiety is drawn in bold), while NPS not yet included in the list of the controlled substances are shown in figure 3.

Cathinones

Most of the samples analyzed were identified as cathinones, in particular 3-MMC and 4-MEC were those that recurred more often, followed by MDPV. The cathinones identified had very similar chemical structures: α-PVP and α-PHP differ only for the length of carbon side chain; as well as the 3,4-methylenedioxy cathinones methylone, butylone and ethylone; 3-MMC, 3-CMC and FMC, are differentiated only by the type of substituent on aromatic ring.
The proposed analytical approach allowed the identification of some cathinones, as α-PVP, α-PHP, bk-2C-B, 3-CMC, MPPP, without the reference standards.
Five samples had the same mass spectra, both in GC/MS and in LC/HRMS, corresponding to 4-FMC (known as flephedrone). Among those samples, three had the same GC/MS retention time of 4-FMC standard but the chromatograms obtained for the other two seizures showed a different retention time with respect to the standard. At the time of the analysis, only 4-FMC standard was available in our laboratory, consequently the position of fluorine atom for the other two isomers was identified by using NMR. The two different isomers of FMC identified were 2-FMC and 3-FMC. NMR analysis allowed the identification of substituent position in absence of standard also for 3-CMC (isomer of 4-chloromethcathinone or clephedrone), and 3-MMC.

Synthetic cannabinoids

Only three seizures of herbal material, all labeled as "herbal blend", contained synthetic cannabinoids. The analysis revealed the presence of AKB48 in one case and in two cases the presence of a mixture in which the major component was 5-fluoro-AKB48 together with traces of BB-22.

Miscellanea

Confiscated substances from other classes were methoxetamine (arylcyclohexylamine), phenethylamines such as 2-fluoromethamphetamine, 4-fluoroamphetamine and methamphetamine (in form of pure crystals or "shaboo"); tryptamines as 5-MeO-DALT and 5-MeO-MiPT; benzofurans as 4-APB and 6-APB, thiophenes as α-PVT and MPA, ethylphenidate (piperidine), 1mCPP (piperazine), MTTA (γ-aminoketone), NM2AI (aminoindane) and diphenidine (diarylethylamine) encountered for the first time in Europe. In 9 seizures were found also tablets containing sildenafil, generally together with cathinones or ethylphenidate.

DISCUSSION

The percentage of compounds seized in the period studied and not included in the list of psychotropic substances is quite high, corresponding to 44% (see figure 4). Anyway, considering

the total number of confiscations, the majority of seizures (80%) were of substances controlled by the Italian law, as shown in figure 5.

The majority of samples from confiscations analyzed in these last two years were related to cathinones group, and therefore controlled by the Italian law, being "analogues derived from 2-amino-1-phenyl-1-propanone", therefore regardless they were isomers of those explicitly cited in the list of psychotropic drugs. This "analogues approach" to include new drugs in the list allowed effective control of the majority of cathinones, even before they were encountered in the Italian illicit marked, since December 2013. This is an important goal, as these kind of substances are a serious threat for the public health [7-10]. In fact we would like to point the attention to the fact that among cathinones, 35 confiscation were constituted of 3-MMC, isomer of mephedrone (4-MMC) and none of them was mephedrone itself. The Italian law includes also 3-MMC, as cathinone analogue, in the list of controlled substances, and therefore it cannot be imported and sold in Italy. A different situation is in other Countries, such as Holland, from which the shipments originated, where the mephedrone molecule is the only controlled, and therefore 3-MMC could, in principle, be prepared, sold and exported without the juridical consequences associated to drugs of abuse. Very recent studies demonstrate how the illicit marked has changed from mephedrone to 3-MMC and how this molecule can be as dangerous as mephedrone itself [7, 8]. MDPV was identified in 19 seizures. The dangers related to the use of this substance are well known [9, 10], and in Italy it was put under control by an *ad hoc* decree in 2011.

On the contrary, some of the molecules identified during the studied period by our laboratory were not controlled by the Italian criminal law yet. Three of the chemical substances seized were synthetic cannabinoids, while 12 compounds belongs to the miscellanea class, as shown in figure 6, being mainly tryptamines, phenethylamines, benzofurans, aminoindanes.

Some of them were analogous of controlled substances, differing only for the position of the substituent (4-APB respect to 6-APB, the latter expressly cited in the list). Another possibility to circumvent the Italian law is the change of some groups in the molecular structure: methylphenidate is included in the list and contains a methyl group, which is substituted with an ethyl one in ethylphenidate; in the controlled substance MDAI there is a methylenedioxy substituent, which is absent in NM2AI. In some cases, such as the controlled substances α-PVP and methamphetamine, an aromatic ring is replaced by a thiophenic ring, obtaining respectively the not controlled α-PVT and MPA. Fluoro-methamphetamine, in the same way, was not included in the list of controlled substances.

Italian law sets under control the three major type of synthetic aminoalkilindole-derived cannabinoids, including in the list of psychotropic substances controlled some expressly cited synthetic cannabinoids and all the analogues derived from 3-phenylacetylindole, 3-(1-naphtoyl)indole and 3-benzoylindole. However in the last years other cannabinoids pertaining to other chemical classes were identified in seizures, like the phenylpyrrole JWH-030 and JWH-307 [11, 12], the cyclopropylindole UR-144 and XRL-11 [12-15], the naphthoylnaphtalene CB-13 [12, 16], the adamantylindole STS-135 and AB-001 [12, 14, 15] and the adamantylindazole AKB-48 [12, 15].

The changes in the illicit marked, probably due to the inclusion of synthetic cannabinoids among the controlled substances since 2010, led to the confiscation of few synthetic cannabinoids in our territory in the last 24 months. We only found three confiscations being AKB48, 5-fluoro-AKB48 and BB-22; being their structure derived from indazole or quinolineindole, none of them is structurally analogue to 3-phenylacetylindole, 3-(1-naphtoyl)indole and 3-benzoylindole and therefore not controlled by the Italian law, although there are studies on the health hazards related to their use [17]. AKB48 is temporarily put under control in the USA due to its potential danger [18].
Among phenetylamines, tryptamines and benzofurans seized and analysed, only "shaboo" (methamphetamine), 4-fluroamphetamine, 6-APB and methoxetamine were controlled by the Italian law even though acute intoxications and fatal cases related to the intake of some of those NPS were reported [19-23].

The approach followed by the Italian law to deal with the continuous changing of the NPS market by the "analogues" legislation seems to be very effective for cathinones, a relatively new class of compounds: the cathinones seized resulted always included in the list of controlled drugs; also for synthetic cannabinoids the approach is quite effective, probably leading to a change of the market that resulted in few confiscations of cannabinoids, none of them controlled by the law.
Different is the situation for other classes of psychotropic substances, such as tryptamines or phenethylamines. In this case, in fact, without the "analogues" approach, not used in Italy for these classes of substances, the new tryptamines and methamphetamine analogues seized cannot be considered as illegal for the Italian criminal law. This underlines the effectiveness of the "analogues" approach in the control of substances potentially dangerous for the public health.

Another potential risk of using these substances is raised by the inconsistency between what declared on the label - or the lack of a label - and the real content, as also reported by other groups [16, 24].
In some cases the seizures had not any label, in other cases were composed of mixtures of NPS not indicated in the label (e.g. 4-MEC + pentedrone + diphenidine, etylphenidate + 5MeO-DALT + caffeine, 5F-AKB + BB22, flephedrone + methoxethamine). The effects of combination of NPS are still unknown and a potential synergic effect has to be taken into account; intoxications related to mixture of NPS are in fact reported in the recent literature [25-27].

CONCLUSIONS

The proposed analytical approach allowed the identification of NPS in 162 seizures, also in absence of an analytical standard. The analyses performed showed the presence in the Italian territory of a wide number of NPS coming from both EU and other Countries (China or Philippines), including substances not controlled by the Italian criminal law yet. The "analogue

approach" adopted in Italy for cathinones showed to be very effective, while some new tryptamines and methamphetamine analogues seized cannot be considered as illegal for the Italian criminal law and need to be included in the list of the controlled substances as soon as possible. This confirms the danger for public health, especially when NPS are sold in combination and when it is not reported the real content of the shipment, and the importance of an early warning system to protect citizens' health.

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FIGURES LEGEND

Figure 1: NPS identified in the period 2013-2015: in the Y axis is reported the number of confiscations for each substance.

Figure 2: Substances identified in the period 2013-2015 included in the list of those controlled by the Italian law. In bold is shown the 2-amino-1-phenyl-1-propanone structure of all the cathinones identified, that automatically includes these substances in the list of those controlled.

Figure 3: Substances identified in the period 2013-2015 not controlled in Italy at the moment.

Figure 4: Percent of the NPS confiscated included in the list of drugs controlled by the Italian law.

Figure 5: Percent of seizures containing NPS included in the list of drugs controlled by the Italian law.

Figure 6: Typologies of seized substances not controlled by the Italian legislation.

Figure 1

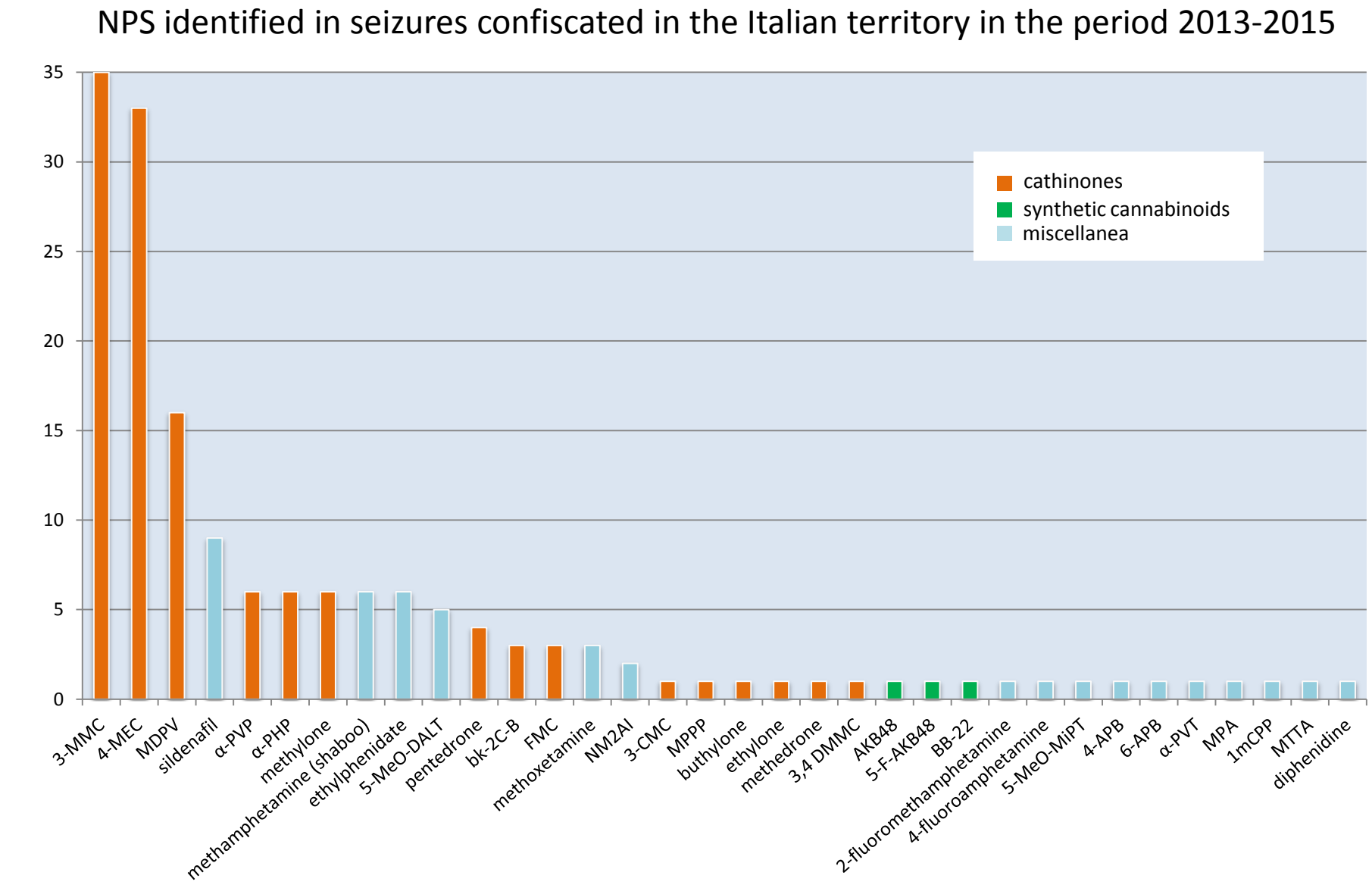
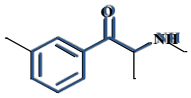
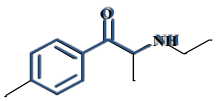

NPS identified in seizures confiscated in the Italian territory in the period 2013-2015
35
30
25
20
15
10
5
0
cathinones
synthetic cannabinoids
miscellanea
3-MMC
4-MEC
MDPV
sildenafil
α-PVP
α-PHP
methylone
methamphetamine (shaboo)
ethylphenidate
5-MeO-DALT
pentedrone
bk-2C-B
FMC
methoxetamine
NM2AI
3-CMC
MPPP
buthylone
ethylone
methedrone
3,4 DMMC
AKB48
5-F-AKB48
BB-22
2-fluoromethamphetamine
4-fluoroamphetamine
5-MeO-MiPT
4-APB
6-APB
α-PVT
MPA
1mCPP
MTTA
diphenidine

Figure 2

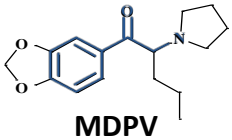
Cathinones



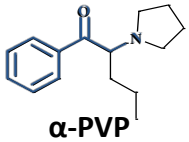
3-MMC
35 seizures



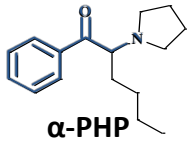
4-MEC
33 seizures



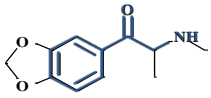
MDPV
16 seizures



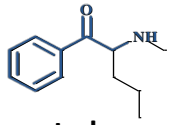
α-PVP
6 seizures



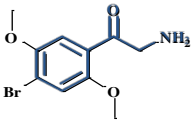
α-PHP
6 seizures



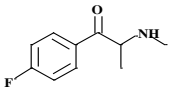
methylone
6 seizures



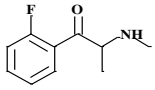
pentedrone
4 seizures



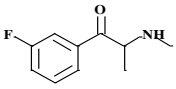
bk-2C-B
3 seizures



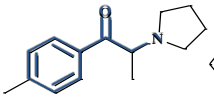
4-FMC
3 seizures



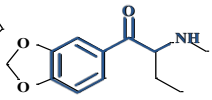
2-FMC
1 seizure



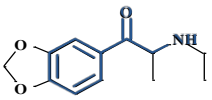
3-FMC
1 seizure



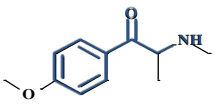
MPPP
1 seizure



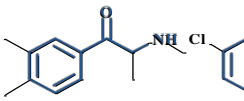
buthylone
1 seizure



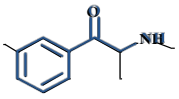
ethylone
1 seizure



methedrone
1 seizure

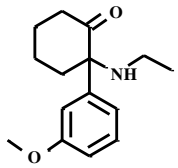


3,4 DMMC
1 seizure

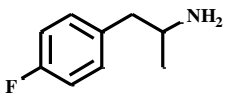


3-CMC
1 seizure

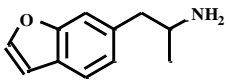
Miscellanea



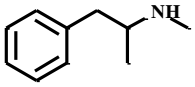
methoxetamine
3 seizures



4-fluoro amphetamine
1 seizure



6-APB
1 seizure

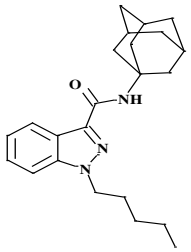


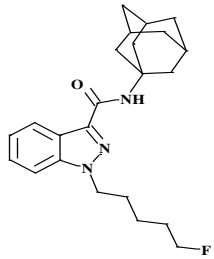
methamphetamine
(shaboo)
6 seizures

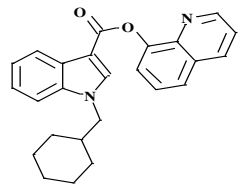
Figure 3

Synthetic cannabinoids

AKB48
1 seizure

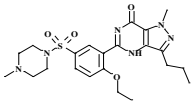




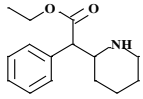


5-F-AKB48 + BB-22
2 seizures

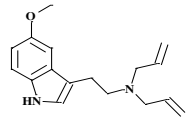
Miscellanea



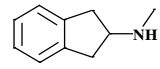
sildenafil
9 seizures



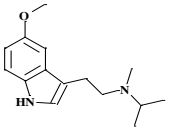
ethylphenidate
6 seizures



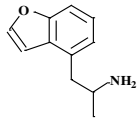
5-MeO-DALT
5 seizures



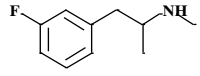
NM2AI
2 seizures



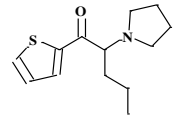
5-MeO-MiPT
1 seizure



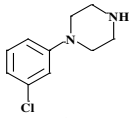
4-APB
1 seizure



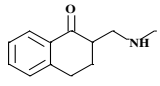
2-fluoro
methamphetamine
1 seizure



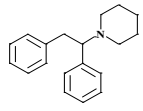
α-PVT
1 seizure



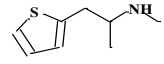
1mCPP
1 seizure



MTTA
1 seizure



diphenidine
1 seizure



MPA
1 seizure

Figure 4

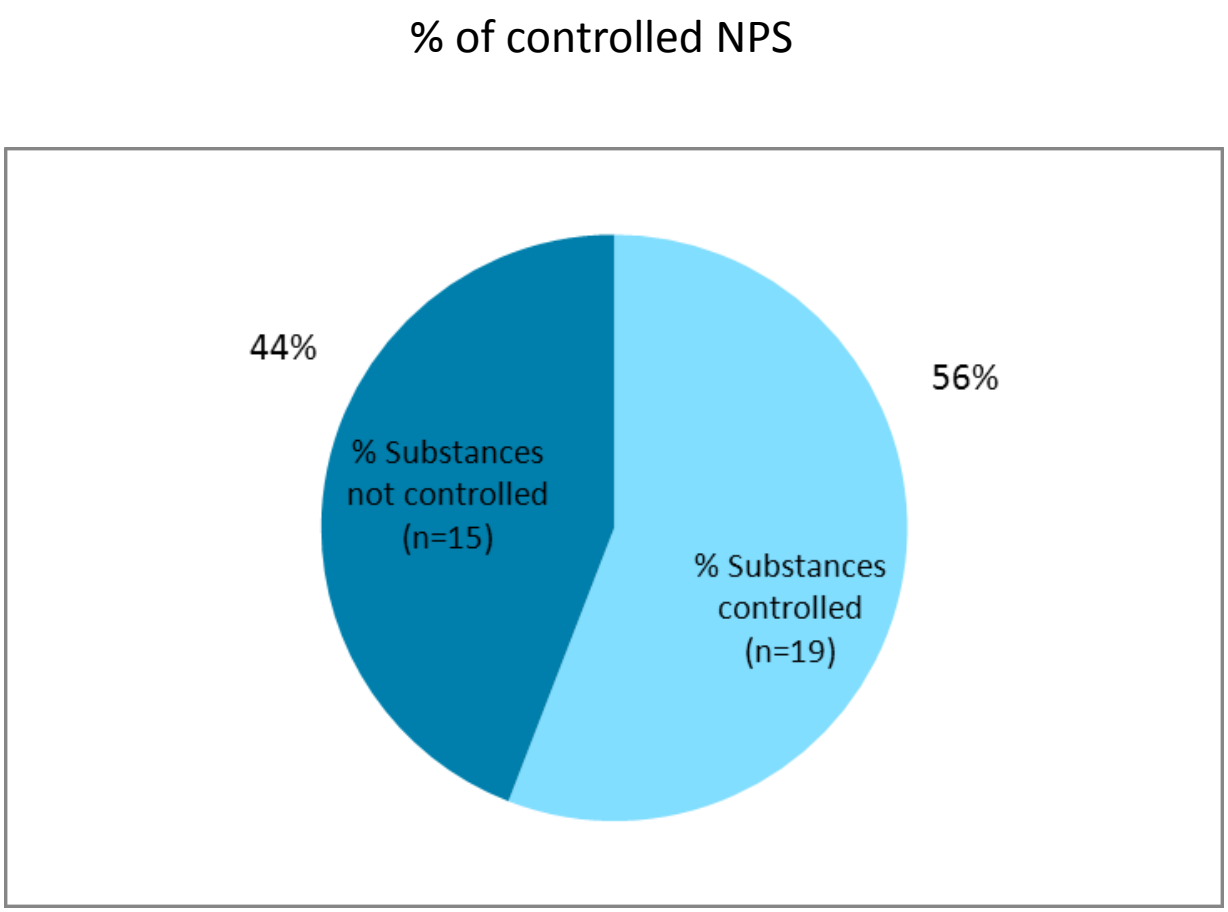

% of controlled NPS
44%
56%
% Substances not controlled (n=15)
% Substances controlled (n=19)

Figure 5

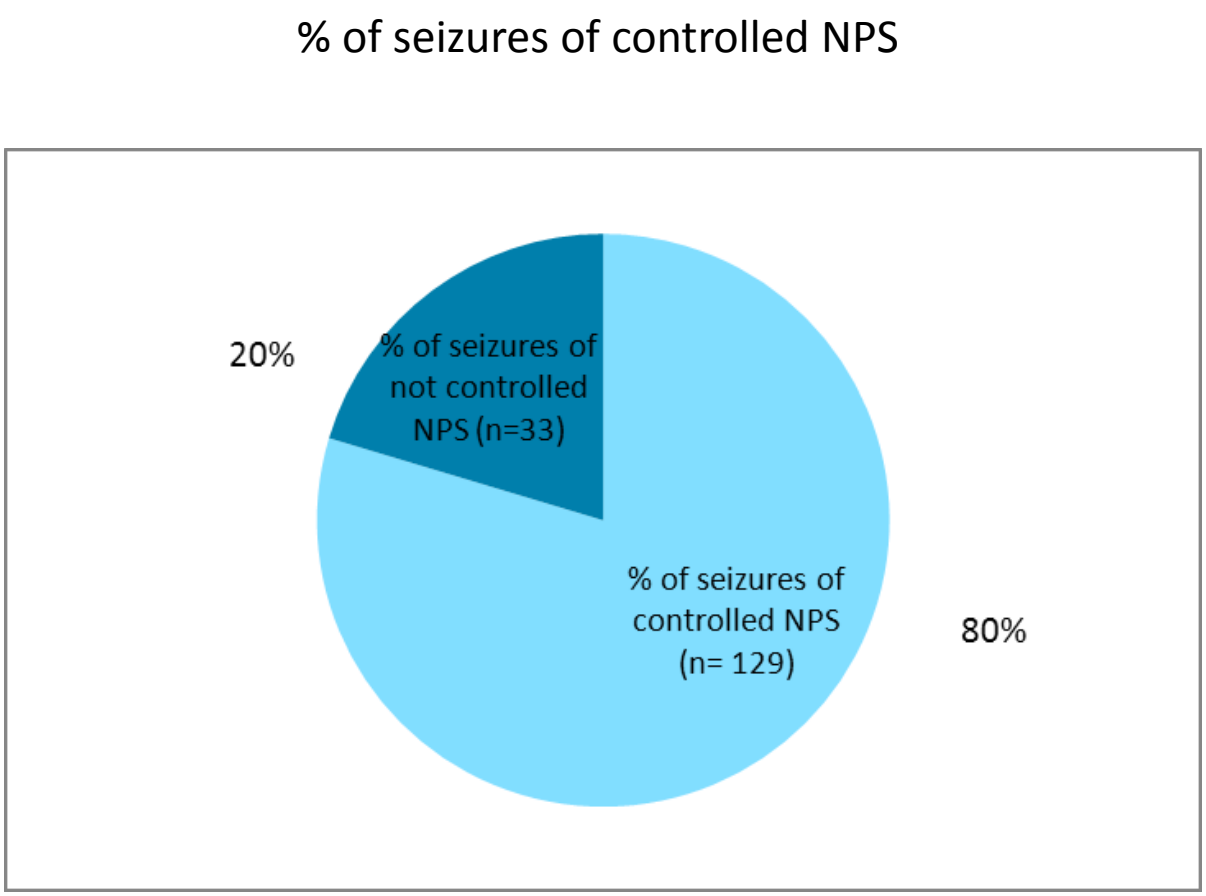
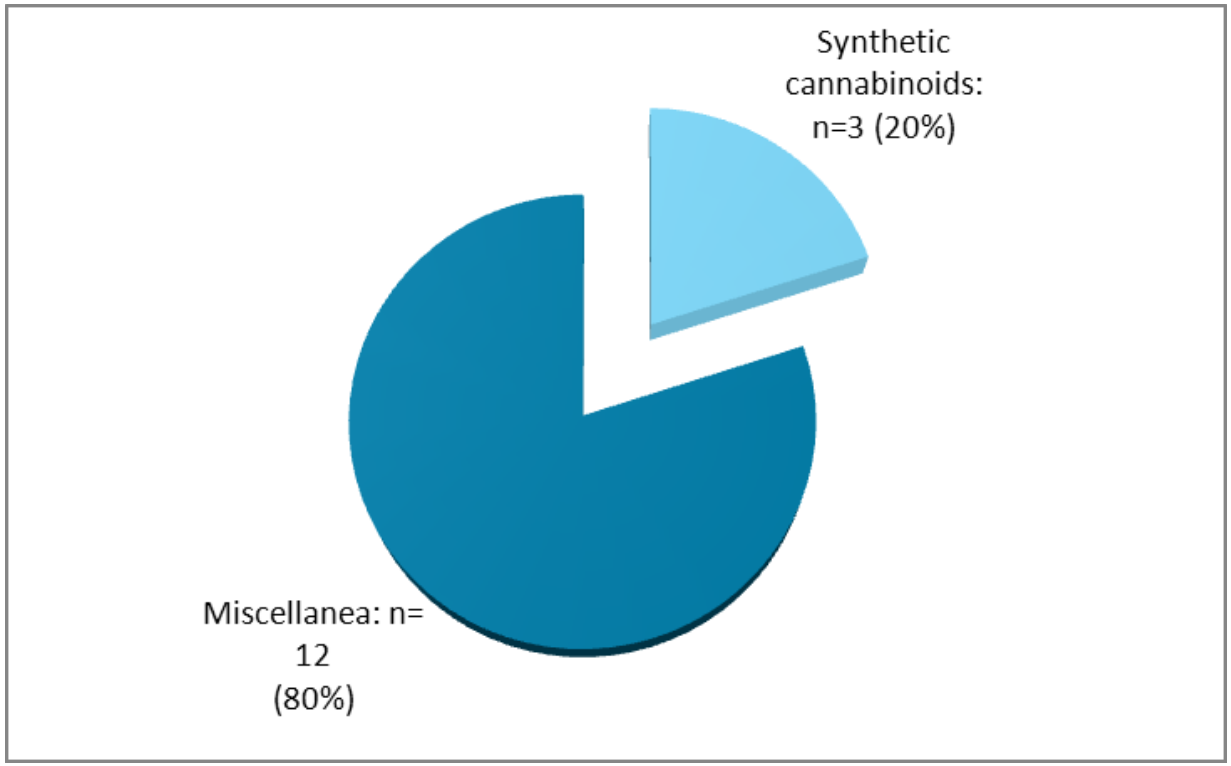

% of seizures of controlled NPS
20%
% of seizures of not controlled NPS (n=33)
% of seizures of controlled NPS (n= 129)
80%

Figure 6


Types of not controlled NPS
Synthetic cannabinoids: n=3 (20%)
Miscellanea: n= 12 (80%)