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Preliminary Detection of New Psychoactive Substances (NPS) in Synthetic Drugs Seizures in the Northeast Brazil in a Period of Two Years (2014–2016)

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Abstract. In the period from 2014 to 2016 a growing number of seizures of synthetic drugs, such as blotter papers, tablets, powders and crystals has occurred in the states of Bahia and Sergipe in the northeast region of Brazil following a worldwide trend. Thus 345 seizures of these materials were performed by local police, leading to the detection of 27 Novel Psychoactive Substances (NPS) classified as phenethylamines, cathinones, synthetic cannabinoids, tryptamines and opioids. Among the previously detected compounds, three cathinones (dimethylone, dibutylone and N-ethylpentylone) and one synthetic opioid (U-47700) are not included in the banned substances scheduled at Ordinance No. 344/98 SVS/ANVISA (an acronym in Portuguese for National Health Surveillance Agency) and updates, making their consumption not prohibited in Brazil. The aim of this work is to report the detection and the emergence of NPS in this region of Brazil, using gas chromatography coupled to mass spectrometry (GC-MS) with updated spectral libraries. This technique has been shown to be an important tool in the preliminary detection of these substances, considering there are no chemical tests available for screening as a preliminary technique. Otherwise, results obtained with GC-MS have been confirmed in an initial study using others analytical tools such as nuclear magnetic resonance (NMR) and infrared spectroscopy (FTIR) as the definitive identification techniques with results that will be published in the near future.

Keywords: New psychoactive substance; Cathinone; Phenetylamine; GC-MS.

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1. Introduction

Seizures of synthetic drugs that is called Novel Psychoactive Substances (NPS) are a worldwide phenomenon and has been growing in recent years. In Brazil more particularly at northeast region the two main classes of these compounds that have been initially detected in different seized materials are cathinones and phenethylamines. Such compounds have been developed and marketed in different forms such as tablets, blotter papers, powders and crystals[1.] According to the World Drug Report 2015, published annually by the United Nations, there has been an increase in the number of NPS identified by member countries that collaborate with the United Nations Office on Drugs and Crime (UNODC) of 243 compounds in 2009 to 519 in the end of 2014. In this period, 327 new substances of different classes were identified for the first time, where cathinones and phenethylamines represented 33% of this total[2]. In Brazil, although there is no official consolidated data on the annual amount of seizures of these substances, it is possible to infer that there is a growing tendency in most Brazilian states, considering the reports of official experts from different institutions responsible for analyzing these materials. In agreement with this affirmation, in the period between January 2014 and August 2016, 27 different psychoactive substances were detected in 345 seizures carried out by the local police in the states of Bahia and Sergipe. Among these, four substances are freely available in Brazil, namely dimethylone, dibutylone, N-ethylpentylone and U-47700 which are not scheduled at Ordinance nº 344/98 SVS/ANVISA and recent updates[3]. Preliminary detection and subsequent identification of these compounds has become a challenging job to forensic laboratories receiving daily seizures of different natures. The main difficulty is related to the analytical ability of unequivocally identifying such substances, in order to distinguish isomers and other molecules with small structural modifications that are sometimes imperceptible in routine analyze[4]. In this way, this work has as main objective to present the variability of NPS detected in the seizures carried out in the last two years (2014 to 2016) in two states of northeast region and to alert to the emergence of some compounds that are not prohibited in accordance with Brazilian law.

2. Experimental procedure

Were analyzed 345 seized samples of tablets, blotter papers, crystals and powders, related to the different seizures. The active principles in the blotter paper samples

were extracted using 1 mL of methanol (Merck, Darmstadt) and taken to the ultrasound for 15 min, injecting 1 µL of the extract into GC-MS. Samples of tablets, powders and crystals were homogenized, added in a microtube with 1.5 ml of methanol, sonicated for 15 min and centrifuged. The GC-MS injection volume was 1 µL in Split mode (50: 1) for all extracts, which were later analyzed on an Agilent model 7890A chromatograph coupled to an Agilent model 5975C mass spectrometer. The column used was HP-5ms (30m x 0.25mm x 0.25µm), Helio was used such as mobile phase with a flow rate of 1mL/min and the heating ramp was set as follows: start at 60ºC for 5 min, 10ºC/min to 240°C. The final temperature was maintained for 15 min (total time 40 min). The mass spectrometer was adjusted with ionization energy of 70eV, using electron ionization (EI+) in the range of m/z 40-550 and acquisition in full scan mode.

3. Results and discussion

Analyzes were performed using GC-MS with mass spectral libraries updated from the SWGDRUG (Scientific Working Group for the Analysis of Seized Drugs) and Cayman Chemical[5,6]. The criteria used in the preliminary detection, considering the similarity of the mass spectra, were values greater than 90% for the Match and Reverse Match indices. These two parameters are used by the NIST Mass Spectral Search software to verify the level of coincidence between the mass spectra of the samples and those present in a library, considering the intensity of the fragments ions and the mass to charge ratio (m/z). The mass spectra compiled in the SWGDRUG library were acquired in the range of m/z 30-550 while in the Cayman library spectra were acquired in the range of m/z 40-550[5,6,17]. The algorithm in the software to find similar spectra uses at least 50 more intense fragments ions in the adjusted m/z range, comparing the proportions between adjacent peaks in the library and the unknown spectra of the samples. In this way, each peak can be represented as a vector in space. The coincidence in the intensity between peaks of the same m/z, considering the unknown spectrum and those added in a library, can be measured by the use of the cosine of the angle between these vectors. The smaller the angle between two vectors the greater the coincidence between them and the greater the similarity index that will approximate to 100%[17]. In view of the analytical approach described it is important to note that the main objective of this study was to perform preliminary NPS detection procedures on seized samples of synthetic drugs. Therefore, no

further investigation was carried out to unambiguously identify the nature of these compounds. Considering all analyzed samples in this study (n = 345) were found compounds of the following classes: 67.6% phenethylamines, 29.6% cathinones, 2.0% tryptamines, 0.6% synthetic cannabinoids and 0.3% opioids, according to Figure 1.

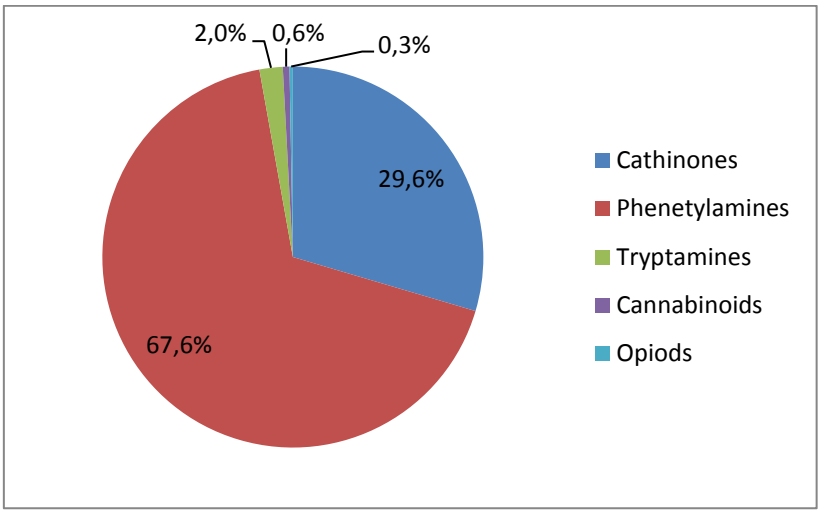


Figure 1. Percentage of seized NPS and their classes in the period from 2014 to 2016.

The variability of compounds detected shows a trend in the illegal market of synthetic drugs in the Brazilian northeast. Considering all 27 compounds found, 16 phenethylamines, 8 cathinones, 1 synthetic cannabinoid, 1 tryptamine and 1 synthetic opioid were preliminarily detected, as shown in Figure 2. These data indicate that, different from what happens in Europe and the United States, other classes of NPS as synthetic cannabinoids and tryptamine have low prevalence, with the exception of N,N-dimethyltryptamine (DMT) found in Ayahuasca, a beverage used in religious rituals and prepared from endemic plants of this region[5,7-11].

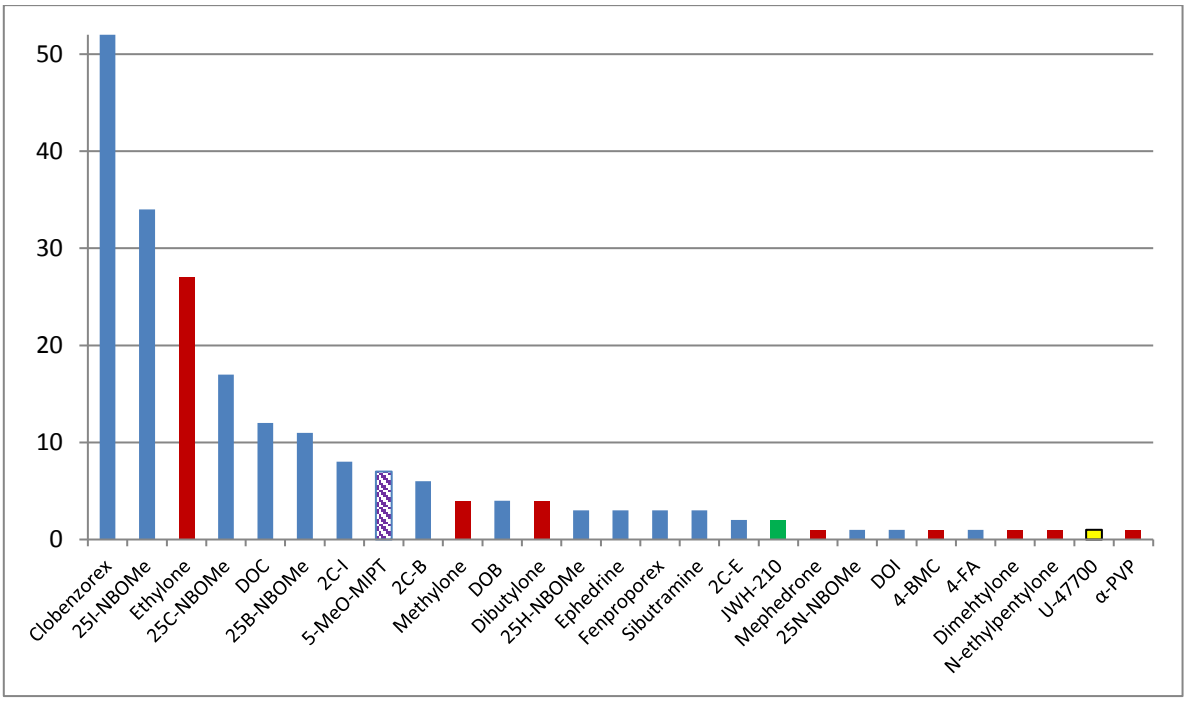


Figure 2. Compounds detected in 345 samples seized in northeast Brazil in the period from 2014 to 2016.

3.1 Phenethylamines and synthetic cathinones

The psychoactive substances classified as phenethylamines were the most prevalent in this study, where sixteen different compounds were detected, as shown in Table 1. Among these, some compounds of the NBOMe family and 2,5-dimethoxy-phenethylamines were found more frequently in blotter paper[12]. Clobenzorex that is widely used as a stimulant by professional drivers on Brazilian roads was the most frequently detected substance in tablets marketed illegally under the name "Nobésio" or "Nobésio Forte". On the other hand, substances used in the past as anorexic drugs and produces stimulant effects, such as fenproporex and sibutramine, were detected in seized tablets, associated with ephedrine[13,14]. Synthetic cathinones compounds formed the second group of NPS with the highest occurrence in the analyzed samples where eight different compounds were detected: methylone, ethylone, dibutylone, dimethylone, N-ethylpentylone, mephedrone, 4-bromomethcathinone and α-PVP. However it is important to observe that some of these compounds are not prohibited in Brazil. Dimethylone, dibutylone and N-ethylpentylone are freely available, considering their unknown nature for Brazilian legislation[3]. These synthetic cathinones are described in the literature as NPS and

are consumed as drugs of abuse in other countries, but only recently have been detected in seizures in Brazil[15].

3.2 Tryptamines

Some tryptamines are classified as neurotransmitters of natural origin and may act as psychoactive hallucinogens found in some plant species, such as serotonin, 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) and dimethyltryptamine (DMT). Other compounds of this class was in the past synthesized for therapeutic purpose but because of the psychoactive effects produced are now consumed as NPS[9,16]. Thus blotter papers and tablets seized and used in this study were analyzed by the presence of 5-methoxy-N-methyl-N-isopropyltryptamine (5-MeO-MIPT) compound in two seizures in Bahia.

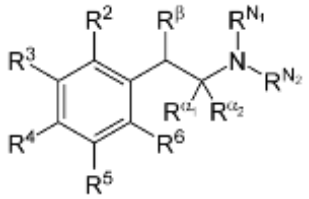
3.4 Synthetic cannabinoids

According to data from the European Monitoring Center for Drugs and Drug Addiction (EMCDDA), synthetic cannabinoids represent the largest NPS group that is monitored on that continent[18]. However, the occurrence of these compounds in the Brazilian northeast is almost non-existent, considering the apprehensions made by the local police in the two states involved in this work. From a total of 345 different seizures analyzed, only two blotter paper samples contained JWH-210, a compound that acts on the so-called cannabinoid receptors and mimics, in some respects, the pharmacological action of Δ^9-THC, the major active ingredient in marijuana[18,19].

3.5 Opioids

The compound U-47700 (3,4-dichloro-N-[2-(dimethylamino)cyclohexyl]-N-methylbenzamide) is classified as an opioid analgesic and has an analgesic power about seven times higher than morphine[20]. Similar tablets to those of ecstasy containing U-47700 were first analyzed in Bahia in a seizure that occurred in 2016. Little information regarding the toxicology of this compound is available in the scientific literature, there being no records for therapeutic use in humans. According to currently Brazilian law, actually this is not a banned substance in Brazil.

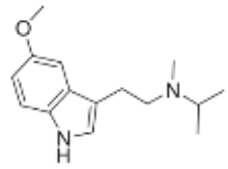
Table 1. Chemical structures of the NPS detected through this study.



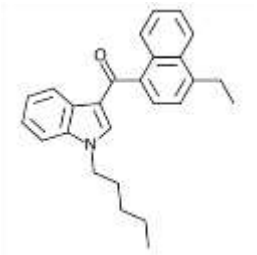
	R2	R3	R4	R5	R6	R_{N1}	R_{N2}	R_{β}	$R\alpha_1$	$R\alpha_2$
Phenethylamine	**-H**	**-H**	**-H**	**-H**	**-H**	**-H**	**-H**	**-H**	**-H**	**-H**
4-FA	-H	-H	-F	-H	-H	-H	-H	-H	$-CH_3$	-H
DOC	$-OCH_3$	-H	-Cl	$-OCH_3$	-H	-H	-H	-H	$-CH_3$	-H
DOB	$-OCH_3$	-H	-Br	$-OCH_3$	-H	-H	-H	-H	$-CH_3$	-H
DOI	$-OCH_3$	-H	-I	$-OCH_3$	-H	-H	-H	-H	$-CH_3$	-H
2C-B	$-OCH_3$	-H	-Br	$-OCH_3$	-H	-H	-H	-H	-H	-H
2C-I	$-OCH_3$	-H	-I	$-OCH_3$	-H	-H	-H	-H	-H	-H
2C-E	$-OCH_3$	-H	$-CH_2CH_3$	$-OCH_3$	-H	-H	-H	-H	-H	-H
25C-NBOMe	$-OCH_3$	-H	-Cl	$-OCH_3$	-H	-H	$-CH_2C_6H_5OCH_3$	-H	-H	-H
25I-NBOMe	$-OCH_3$	-H	-I	$-OCH_3$	-H	-H	$-CH_2C_6H_5OCH_3$	-H	-H	-H
25B-NBOMe	$-OCH_3$	-H	-Br	$-OCH_3$	-H	-H	$-CH_2C_6H_5OCH_3$	-H	-H	-H
25H-NBOMe	$-OCH_3$	-H	-H	$-OCH_3$	-H	-H	$-CH_2C_6H_5OCH_3$	-H	-H	-H
25N-NBOMe	$-OCH_3$	-H	$-NO_2$	$-OCH_3$	-H	-H	$-CH_2C_6H_5OCH_3$	-H	-H	-H
Clobenzorex	-H	-H	-H	-H	-H	-H	$-CH_2C_6H_5Cl$	-H	$-CH_3$	-H
Fenproporex	-H	-H	-H	-H	-H	-H	$-CH_2CH_2CN$	-H	$-CH_3$	-H
Sibutramine	-H	-H	-Cl	-H	-H	-H	$-CH_2C_6H_5Cl$	$-(CH_2)_3-$	$-CH_3$	-H

Ephedrine	-H	-H	-H	-H	-H	-H	$-CH_3$	-OH	-H	$-CH_2CH(CH_3)_2$
Cathinone	**-H**	**-H**	**-H**	**-H**	**-H**	**-H**	**-H**	**=O**	**-H**	**-H**
Methylone	-H	$-OCH_2O-$		-H	-H	-H	$-CH_3$	=O	-H	$-CH_3$
Ethylone	-H	$-OCH_2O-$		-H	-H	-H	$-CH_2CH_3$	=O	-H	$-CH_3$
Dibutylone	-H	$-OCH_2O-$		-H	-H	$-CH_3$	$-CH_3$	=O	-H	$-CH_2CH_3$
Mephedrone	-H	-H	$-CH_3$	-H	-H	-H	$-CH_3$	=O	-H	$-CH_3$
4-BMC	-H	-H	-Br	-H	-H	-H	$-CH_3$	=O	-H	$-CH_3$
Dimethylone	-H	$-OCH_2O-$		-H	-H	$-CH_3$	$-CH_3$	=O	-H	$-CH_3$
N-ethylpentylone	-H	$-OCH_2O-$		-H	-H	-H	$-CH_2CH_3$	=O	-H	$-CH_2CH_2CH_3$
α-PVP	-H	-H	-H	-H	-H	$-CH_2CH_2CH_2CH_2-$		=O	-H	$-CH_2CH_2CH_3$

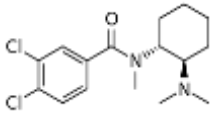
Other compounds



5-MeO-MIPT (*tryptamine*)



JWH-210 (*synthetic cannabinoid*)



U-47700 (*opioid*)

4. Conclusion

Twenty-seven new psychoactive substances were preliminary detected in 345 samples seized in different forms of presentation such as tablets, blotter papers and powders. All the compounds detected have been previously described in the literature and their elucidated structures, since these have available analytical data that aid in the identification. The use of updated mass spectra libraries was essential to aid in the detection of these substances, considering the diversity of compounds and the few structural differences between them. It is important to note that the identification information acquired with GC-MS is only preliminary and serves to indicate more precisely which chemical structure can be confounded using other analytical techniques such as infrared spectroscopy (FTIR), high resolution mass spectrometry (HR-MS) and nuclear magnetic resonance (NMR), whereas there are few established chemical tests for preliminary detection of these psychoactive substances[21]. On the other hand the use of this tool as a screening technique for

synthetic drugs has proved to be quite robust when using updated mass spectra and the knowledge of an experienced analyst[22]. Thus it is imperative to closely observe and interpret the small differences that exist between fragmentation profiles of mass spectra that appear to be similar. After the preliminary analysis of this set of samples, it was possible to infer that the diversity of synthetic drugs and the increasing number of seizures in Brazilian northeast are of great importance due to the economic reality of this region, considered one of the poorest in Brazil and with the the lowest Human Development Index (HDI), according to data from the Brazilian Institute of Geography and Statistics (IBGE)[23]. The consumption of synthetic drugs is related to regions and population groups of greater purchasing power, because it costs more expensive than other more popular and cheap drugs like crack and marijuana. In view of this, it is important to consider the growing trend in the regional distribution of these drugs and the possible consequences related to public health and addiction, because little information about the toxicology of these substances is available in the scientific literature.

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