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New psychoactive substances (NPS) prevalence over LSD in blotter seized in State of Santa Catarina, Brazil: A six-year retrospective study

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ABSTRACT

Designer drugs or new psychoactive substances (NPS) are a heterogeneous group of substances obtained through the modification of chemical structure of some natural products or drugs. NPS illegally commercialized in blotter papers mimicking the most common form of LSD consumption, with a great variability of colours and symbols, have largely increased worldwide, including in Brazil, becoming an important emerging public health issue. In this study, we have evaluated the presence and profile of NPS in blotters seized in the State of Santa Catarina, Brazil, over the period of 2011 to 2017. The state government criminal forensics staff has performed gas chromatography-mass spectrometer (GC–MS) analyses in order to determine the chemical composition of the blotters. During the evaluated period, there was a considerable increase in the seizing of blotters events, from 87 in 2011, to 301 in 2016 and reaching 277 in 2017. There was also an increase in the number of blotters seized per event. Interestingly, while in 2011, 100% of blotters contained LSD, this number decreased to 0,1% in 2014, and achieved 17,6% in 2017, when up to 25 different substances were detected in blotters seized. Drugs such as DOx, NBOMe, fentanyl, mescaline derivatives, triptamines, cathinones, and synthetic cannabinoids were detected and became the major substances found in blotters. In some cases, more than one substance was found in the same blotter, characterizing a new mixture scenario. The presence of several new psychoactive substances in blotters is a reality in forensic toxicology. In Brazil, it might be related to the fact that most of these substances were not considered illegal by Brazilian legislation by the time they emerged.

1. Introduction

Although until recently the main hallucinogen found in seized blotters was LSD, other substances have been identified in this matrix. Similarly to what has been seen in ecstasy-like tablets [1], the chemical content of these blotters is diverse. In recent years, spreading of new and unregulated substances of abuse, referred generally as new psychoactive substances (NPS), also known as novel designer drugs or legal highs (an allusion to the deceptive legal status of such substances on most countries), has become a public health issue, demanding constantly updated knowledge about the chemistry, pharmacology and toxicology of these substances [2,3]. Since the monitoring of NPS through the United Nations Office on Drugs and Crime (UNODC) Early Warning Advisory (EWA) began in 2009, an increasing number of NPS are being classified as hallucinogens and dissociative-anaesthetics. In 2017, hallucinogen NPS accounted for 18% of the total of 492 NPS reported [4]. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) has monitored more than 670 new psychoactive substances, with 51 substances been reported for the first time in 2017 [5].

In Brazil, a substance must be included in the National Sanitary Surveillance Agency (ANVISA) List F of Proscribed Substances (RDC 344) to be considered illegal. Among the new substances detected in blotters, some could circulate freely as they were not part of the Brazilian legislation. Unfortunately, there is not a centralized database of NPS and/or synthetic drugs seized in Brazil that includes all the States. There are few data publicly available about Brazilian seizures of NPS provided by Federal Police, or State Polices. However, as most seizures are conducted by State Police, and there is not a central collection/compilation of drug seizures of each State, the overall country-wide perspective is not clearly pictured. A retrospective study conducted by Forensic Chemistry

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Laboratory of Minas Gerais State Police between May 2008 and December 2017 detected 93 different substances in seized materials including tablets, blotter papers, crystals and powders. Of these substances, 62 were classified as NPS and 10 as synthetic substances under international control (non-NPS) [6].

Patients intoxicated with NPS represent a significant burden to the healthcare system, especially the emergency medical care. Acute effects include agitation, hallucination, psychosis, violent behaviour, coma [7], and even death [8]. The long-term consequences of NPS exposure are not known but are associated with the onset of psychopathological consequences [9].

Despite the toxicity of these emerging drugs of abuse and recent regulatory efforts, use of new hallucinogenic drugs remains largely unabated. Drugs of abuse can be easily bought on the internet, without prescriptions or legal restrictions [10,11]. Besides, the formulation changes quickly, with different drugs being added to blotters, and the several brand names add complexity for forensic and public health investigations. Therefore, the aim of this work was to evaluate the change in the profile of substances and the presence of NPS in blotters seized in the State of Santa Catarina (Brazil) during the period of 2011–2017.

2. Material and methods

2.1. Chemicals and reagents

Ethyl acetate was purchased from Sigma-Aldrich (St. Louis, MO, USA), ammonia 30% from PanReac AppliChem (Barcelona, Spain). Certified analytical reference standards of cocaine, fentanyl, ketamine, LSD, MDMA, 25B-NBOMe, 25C-NBOMe, 25I-NBOMe, DOB and DOC were obtained from Cerilliant Corporation (Round Rock, TX, USA).

2.2. Samples

Blotter papers suspected to contain illicit substances were seized between 2011 and 2017 by Local Police Forces of the State of Santa Catarina, Brazil, and processed by the Instituto Geral de Perícias (IGP) state government criminal forensics staff. These blotters presented a colorful side decorated with different artwork patterns including drawings of famous celebrities, cartoon characters, Hindu gods/goddesses, etc. (Fig. 1) and a blank side, which sometimes displayed a chemical structure. The sampling criteria followed the United Nations Office on Drugs and Crime's (UNODC) recommendations [12]. For counting criteria, each blotter was considered as one drug unit.

Blotter chemical substances were extracted using 500 μL of ethyl acetate. To alkalinize them, one drop of 30% ammonia was used. Samples were vortex-mixed for 15 s and centrifuged for 3 min at 3500 x g. The organic phase (1 μL) was directly injected into the gas chromatography-mass spectrometry (GC–MS) system.

2.3. Instrumental

GC–MS analyses were performed by an Agilent 7890 Gas Chromatograph coupled with an Agilent 5975C quadrupole mass selective detector (Agilent Technologies, USA). The chromatographic column used was a HP-5-MS capillary column (30 m × 0.25 mm × 0.25 μm film thickness, Agilent J&W GC Columns, USA). The oven temperature program started with an initial temperature of 100 °C and initial hold time of 0 min. Then temperature increased to 300 °C at a rate of 15 °C/min, and held for 5,5 min giving a total of 17,9 min run-time. Helium was used as carrier gas at a constant flow of 2 ml/min. CG injection port was set at 280 °C in splitless mode. Transfer line temperature was set at 300 °C. The mass detector operated in electron ionization at 70 eV in full-scan mode. Full scan acquisition range was *m/z* 30–550.

Substance identification was performed by direct comparison with reference standards. All other substances were identified by computer based spectrometric library search using the following commercial libraries: Wiley Registry 9th Edition/NIST 2011 Mass Spectral Library, Mass Spectral Library of Drugs, Poisons, Pesticides, Pollutants and Their Metabolite; Maurer, Pfleger, Weber; "MPW library" 2011 and SWGDRUG last edition. It was not detected

Fig. 1. Representative images of seized blotter papers.

any chromatographic peak that has not been identified, using the methodology described.

3. Results and discussion

A total of 1,144,143 blotters decorated with different artwork patterns were taken from 1385 apprehensions conducted by Local Police Forces on the State of Santa Catarina, Brazil, and received by the state government criminal forensics staff of the Instituto Geral de Perícias (IGP) over the period of 2011 to 2017. It was observed a progressive increase in the number of apprehensions, from 87 in 2011 to 277 apprehensions in 2017, as can be seen in Fig. 2. The samples were analyzed by gas chromatography coupled with mass spectrometry (GC–MS). In 1,007,235 blotters, no chromatographic peaks were detected, and those samples were considered negative. In 136,822 blotters at least one substance was detected (Table 1). Only these positive samples were considered for evaluation of the chemical profile (Table 2).

By default, all the blotters seized by Santa Catarina State Police are sent for forensic analysis. Noteworthy, while in 2011 LSD was the only substance detected in blotter samples, 25 different substances were identified in 2017. According to Table 2, it is possible to notice a decrease in blotters containing LSD, with an increase of blotters containing new psychoactive substances. This phenomenon started in 2012 and was particularly noted in 2014, when LSD was detected in less than 1% of the samples. Among these other substances, the amphetamine derivatives DOB and DOC, opiods such as fentanyl, 3-furanilfentanyl, and U-47700, NBOMe compounds, and synthetic cannabinoids (AMB-FUBINACA and ADB-FUBINACA) were detected. Furthermore, the analysis showed the presence of blotters containing either only one substance or mixtures. Therefore, in Table 2, substances are listed as the percentage of positive blotters in which they were identified. Some detected substances like dipyrone, lidocaine, caffeine, etc. are considered cutting agents, and are not under legal control.

A timeline of the appearance of NPS in blotters seized in the State of Santa Catarina is depicted in Fig. 3. It is interesting to notice that some of them were not even under legal control by the time they were first detected, and some of them actually remained in this situation for a long time until they were finally added to the ANVISA List F of Proscribed Substances (RDC 344).

The literature reports the presence of psychoactive substances other than LSD in blotters is rare. Despite of that, DOB, that usually is consumed in capsules, was already detected in blotters seized in Italy [13]. Unlike LSD, DOB can have physically harmful, sometimes fatal, side effects which could induce overdose [14]. As DOB, DOC is an amphetamine designer drug that has similar effects to other amphetamines, including tachycardia, hypertension, anion gap acidosis, rhabdomyolysis, tremors, and seizures [15]. As shown in Table 2, DOB was the main substance (besides LSD) detected in blotters in Santa Catarina in 2012. DOC and DOB together were present in approximately 80% of the blotters seized between 2013 and 2014, overtaking the lead frequency of LSD identified previously in 2011 and 2012.

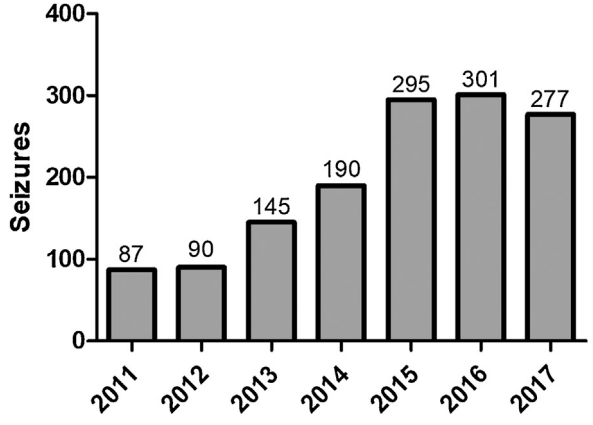

Fig. 2. Chart: Number of apprehensions of blotters in the State of Santa Catarina (Brazil) over the period of.2011–2017.

Table 1
Number of blotter papers in which at least one substance was detected (positive) and none substance was detected (negative) in the period of.2011–2017.

Samples	2011	2012	2013	2014	2015	2016	2017
Positive	9145	5131	7453	27680	28350	30067	28996
Negative	4	0	0	8	29635	9228	968360
Total	9149	5131	7453	27688	57985	39295	997356

The NBOMes, which are a generic denomination for phenethylamines presenting a 2-methoxybenzyl group replacing a hydrogen on the amine, were first detected in 2014 and have been attracting attention from medical and legal authorities [16]. Blotter papers and powders containing these substances were first reported in Poland in 2011 [17] but they were also detected in the USA [18]. Due to the lack of comparative toxicological data, it is difficult to attribute differences in the potency and toxicity of each NBOMe. Indeed, it is not possible to say that one variant is more dangerous or more likely to produce serotonin toxicity than another [19]. The NBOMes were detected in 10% of the blotters seized in 2014 and this number increased to 50% in 2015. In 2016, the NBOHs (25I-NBOH, 25C-NBOH e 25B-NBOH) emerged, being present in two thirds of the total blotters seized in that year and in half of the blotters seized in 2017. The 25I-NBOH was the most frequent derivative in these two years.

According to the latest Brazil National Alcohol and Drugs Survey performed in 2014, the use of hallucinogens was reported by 1.4% of teenagers and 0.9% of adults [20]. However, the first detection of NBOMes was in 2013, making the knowledge of the real consumption of these substances not clear. In spite of that, there are case-reports and even deaths related to NBOMes use in Brazil [21,22].

NBOMEs and NBOHs are still considered legal in some countries, which seems to be related to the increased use of such substances and even encouraging commerce of NBOMEs as counterfeit LSD [23]. Blotters sold as LSD, but containing NBOMEs or NBOHs instead, have been found in Spain, Austria, Brazil, Chile, Colombia and possibly other countries [23–27]. Similar to LSD, they act as partial or full 5-HT_{2A} receptor agonists [28,29], producing hallucinogenic effects. They appear to be active at low doses (50–250 μg) and a typical dose ranges from 500 to 800 μg [16]. Its undesirable effects include tachycardia, hypertension, agitation, confusion, pupil dilation, aggressiveness and seizures [30–32]. NBOMEs are much more dangerous and potentially fatal when compared with LSD [33,34]. A user who is specifically attempting to make use of LSD may ingest NBOMe without been aware of the threatening risks [35].

Fentanyl was first detected in blotters in the State of Santa Catarina in 2017 and it was identified in 12.3% of the blotters seized in that year. These opioids associated with misuse by healthcare personnel, such as physicians (notably anesthesiologists), nurses, pharmacists and ancillary staff who have easy access to the substance. However, alarming epidemiological and forensic medicine reports point to a growing increase in illicit fentanyl use by opioid abusers, including subjects on opioid maintenance treatment. Following the synthesis of fentanyl in late 1950s, several analogues of this drug were designed [36]. Some of them were registered for use in humans (alfentanil, remifentanil, sufentanil, and lofentanil) and in veterinary medicine for wild

Table 2
Chemical substances found in blotters seized in the State of Santa Catarina (Brazil) over the period of 2011–2017 (in bold the three most frequent substances in each year).

Psychoactive drug	2011	2012	2013	2014	2015	2016	2017
LSD	**100%**	**89.3%**	**16.9%**	0.12%	1.2%	**5.8%**	**17.6%**
DOB		**9.2%**	**29.8%**	**37.1%**	2.2%	2.3%	0.12%
5-MeO-NIPT		0.17%					
25B-NBOMe			0.8%	1.5%	7.1%	2.1%	0.86%
Cocaine		**0.47%**	2.01%	6.39%	0.19%	1.94%	0.56%
MDMA		0.39%		**12.84%**	**39.25%**	0.24%	0.7%
Ketamine		0.12%	1.45%	10.92%	**39.46%**		
Clobenzorex		0.31%	0.26%				
25B-NBOH							1.4%
Ergometrine			0.01%		0.02%	0.01%	
DOC			**37.9%**	**40.4%**	6.6%	**6.4%**	1.7%
25I-NBOMe			9.8%	6.3%	**41.4%**	10%	4.2%
25C-NBOMe			0.3%	1.5%	1.6%	0.12%	0.2%
25H-NBOMe				0.06%			0.2%
DMA			2.3%	0.12%			
Methallylescaline				0.01%	0.7%		
Ethylone				1.06%			
Fentanyl						4.7%	**12.3%**
U-47700						0.07%	0.12%
25I-NBOH						**62.2%**	**49.9%**
TH-PVP						0.05%	
25D-NBOMe						0.05%	
25C-NBOH						4.1%	
25I-NBF							0.07%
3-Furanylfentanyl							2.4%
AMB-FUBINACA							0.3%
ADB-FUBINACA							0.04%
DOI							3.7%
MPCP							3.3%
4-MEC							0.02%
Dibutylone							0.01%
n-Ethylpentylone							0.03%
Cutting agents							
Benzydamine		0.32%					
Diazepam		0.04%					
Lidocaine		0.11%	1.78%	6.22%	0.01%		
Caffeine		0.27%	1.45%	10.73%	0.21%		
Levamisole			1.45%				
Dipyrone				6.99%	0.36%		
Phenacetin				5.04%			
Tramadol							0.35%
Total of positive blotters	**9145**	5131	7453	27680	28350	30067	28996

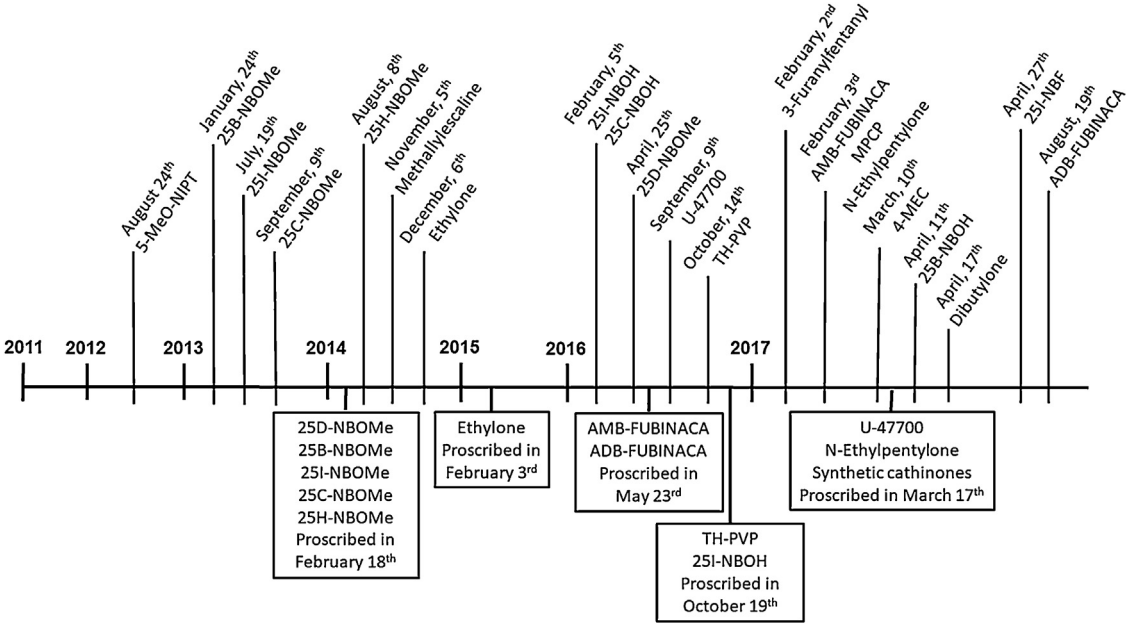

Fig. 3. Timeline of the dates of the first detection (above) of the substance and the date of proscription (below).

animals (carfentanil and thiofentanil), while others (e.g., acetylfentanyl, acryloylfentanyl, butyrylfentanyl, cyclopentylfentanyl, furanylfentanyl, octofentanyl, AH-7921, U-47700, and MT-45), the so called non-pharmaceutical fentanyls or fentalogs, were never developed into a medicinal product [37].

Fentanyl analogs have been found in the form of powder, liquids, tablets, and herbal material. Blotter papers have not been reported as a common form to commercialize it yet, even though they are easy to transport and to sell [38]. In some parts of the world, such as the USA [39] and Australia [40], opioids abuse has gained an epidemic status [41]. Factors contributing to the proliferation of fentanyl analogs and novel synthetic opioids may include the ease of availability – synthetic opioids are relatively easy to produce when compared to heroin -, profitability, and increasing restrictions on prescription of opioids [42,43].

Interestingly, to the best of our knowledge, the presence of other drugs such as synthetic cathinones, tryptamines, and synthetic cannabinoids in blotters has not been reported yet. Synthetic cathinones (TH-PVP, 4-MEC), often marketed as bath salts or plant feeders, are generally sold in the form of a white or yellowish amorphous or crystalline powder, or in capsules. Their presence in tablets, as well as in blotters, is uncommon [44]. Similarly, tryptamine derivatives are typically sold in the form of tablets or powders, as free base or salt. *N,N*-Dimethyltryptamine (DMT) is not orally active due to extensive first-pass metabolism, probably through the rapid action of MAO enzymes in the gut and liver, and is therefore typically used by inhalation or insufflation. In contrast, the amine nitrogen alkyl substituents in DMT result in its homologs, such as N-isopropyltryptamine (NIPT), that are orally active, being the preferential route of administration [45].

Synthetic cannabinoids are the fastest growing class of NPS in USA, Europe, Australia, New Zealand and Japan [46–48] and their use has increased in the adolescent age group [49]. Typically, they are dissolved in solvent, applied to an inert herbal substrate, and smoked in a fashion similar to cannabis. The powder form is normally white but it can be of other colours and it tends to be packed in bags with information about the composition, weight and purity. Labels specifying that the content is “not suitable for human consumption”, “for laboratory use only”, or “for technical use only” are often present [50]. AMB-FUBINACA and ADB-FUBINACA are potent indazole synthetic cannabinoids that reflect the continued evolution of chemical structures of cannabinoid receptor agonists [51]. In the State of Santa Catarina both synthetic cannabinoids were found exclusively in blotter papers and were first detected in 2017.

NPS are being continuously detected in seized materials. Safety data on toxicity and lethality of many of these chemicals are scarce or non-existent and long-term toxicity and risks are still largely unknown. In addition, purity and composition of products containing NPS are often inconsistent or not known, which puts users at a high risk as evidenced by hospital emergency admissions and deaths, sometimes as a result of polysubstance use [50].

4. Conclusion

The occurrence of new psychoactive substances in paper blotters is a reality and a challenge in the forensic toxicology field. Specially in Brazil, it might be related to the fact that most of these substances were not considered illegal by Brazilian legislation by the time they emerged. This also represents a challenge for analytical toxicologists, who must be prepared to detect these substances considering their increase in the previous years and the growing complexity of blotter analysis. Besides that, attention should be given to the recreational use of new and unknown substances. The unpredictability of illicit drug synthesis regarding chemical purity, composition and concentration may differ substantially, making it difficult to predict the wide range of harmful effects of these substances.

CRediT authorship contribution statement

Bruna de Souza Boff, Jair Silveira Filho, Karina Nonemacher, Samilla Driessen Schroeder, and Kéttulin Zomer Rezin were responsible for chemical analysis of the samples. All authors contributed to the conceptualization, data curation and formal analysis of the manuscript.

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