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Synthetic illicit opioids in Brazil: Nitazenes arrival

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ABSTRACT

Purpose: While illicit opioids have not been historically significant in Brazil, these numbers have increased in the last few years. This change in the drug scenario is mainly associated with synthetic opioids, a class of new psychoactive substances (NPS). In this context, the present article describes detailed information about the recent cases of synthetic opioids seized in Brazil, especially the nitazenes group.
Methods: All the analyses were carried out by the Superintendence of the Technical-Scientific Police - Narcotics Control Center (STSP-NCC) in São Paulo, between July 2022 and April 2023. The synthetic opioids were mainly found in herbal fragments.
Results: Nitazenes, were the most frequent drugs detected in the seizures that took place in the State of São Paulo. There was a total of 140 cases of opioids seizures and 95 % out of those belonging to the nitazene group, while only 5 % consisted of other opioids (morphine and fentanyl). Nitazenes were found 28.6 % isolated and 71.4 % mixed with other active compounds, being MDMB-4en-PINACA the most prevalent (30 % of the samples). Non-nitazenes were found 27.1 % mixed and 72.9 % isolated. Nitazenes and non-nitazene opioids were not found in association in any sample.
Conclusion: This is the first consistent report of nitazene opioids apprehensions in Brazil. Also, as far as we know, it is the first report in which nitazenes were detected in the form of herbal fragments. The effect of smoking a potent opioid together with synthetic cannabinoids is unpredictable and most users cannot be aware of what they are using.

1. Introduction

Opioids are an important medication used for pain treatment due to their efficient pharmacological properties despite having a concerning addictive potential These features make opioids valuable and necessary medications with certain risks to be considered whenever prescribed [1]. Furthermore, when looking at the amount of opioid overdose-related deaths over the past few years in the U.S., the number of cases rose from 21,089 in 2010–81,806 in 2022 [2,3]. In addition, before the onset of coronavirus pandemic lockdowns, a striking increase in deaths caused by synthetic opioids was observed in contrast to morphine and heroin, reaching 71,500 cases by January 2022 [3–5].

Opioid-related deaths are usually associated with classic opioids, such as methadone and morphine. This definition was established to differentiate those substances from the new synthetic opioids, a class of new psychoactive substances (NPS). These novel compounds mimic the effects of classic opioids but are chemically different. As a result, these novel chemicals are sold as legal alternatives to classic opioids and thus averting legal control [2].

As threatening as this opioid epidemic scenario is, it does not seem to affect all countries to the same extent. For example, the number of opioid seizures and intoxications in Brazilian territory has always been low. When analyzing previous studies on the use of synthetic opioids in this country, which are scarce, it becomes evident that the focus of such studies was not the misuse of opioids, as it was considered negligible [6]. On the other hand, the study of Maia et al., 2021 concluded that only 111 of all deaths related to psychoactive substances were associated with opioids between 1998 and 2018, representing 0.08 % out of all

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psychoactive substance-related deaths in Brazil. When compared to other American countries, especially the U.S., the lowest number of narcotics abuses was observed in the Brazilian territory, which can be attributed to socioeconomic factors, medical and patient education policies, and the current legal control for prescribed substances, among others. In that regard, the most frequently abused substances in Brazil are stimulants (mainly cocaine/crack), cannabinoids, and hallucinogens [7]. However, this trend has been changing in the last years, as the increase in sales of prescribed opioids and the seizures of synthetic opioids by the police in São Paulo raise an old concern about the abuse of these substances in the country. [6]

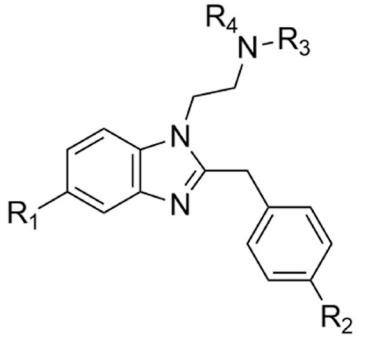
Due to the increasing consumption of so-called synthetic opioids, this scenario has become relevant in the global opioid pandemic situation [2]. Of this NPS class, one group of substances that have been gaining attention due to increasing prevalence among drug users is the nitazenes. Synthesized by a Swiss company that was searching for safer analgesic opioids to be used in pharmacological treatments, the nitazene group was discovered in the mid-50 s [8]. These compounds are highly potent μ-opioid receptor (MOR) agonists with heroin-like effects having a potency around 10−15 times higher (e.g. metonitazene, isonitazene, protonitazene) or even 20 times higher (e.g. etonitazene) than fentanyl [2]. The core structure of this group consists of a benzimidazole core and an amine tail, which give origin to different compounds depending on the chemical modifications. As illustrated in Fig. 1, benzimidazoles are chemically different from morphine, piperidylthiambutene, fentanyl, or other synthetic opioids mainly because of this characteristic core. Thus, starting from a main structure, it is possible to obtain a plethora of similar molecules by introducing minor to mild chemical modifications, while retaining the main MOR agonist effects. However, it was soon discovered that these newly synthesized nitazenes caused dose-dependent respiratory depression and had a high risk of abuse and toxicity [9]. Curiously, even the famous chemist Alexander T. Shulgin, known to have discovered and tested hundreds of psychoactive compounds, warned about the strong potential for misuse that this nitazene group of MOR agonists represented [8].

Since their original synthesis in the 1950s, there have been only a few reports describing nitazenes in the world illicit drug market. For example, etonitazene was only found in some cases between the years 1966 and 2003, while isonitazene was found being commercialized for illicit purposes in Canada and Europe (Germany, United Kingdom, Latvia) in 2019, leading to its report to the U.S. *NPS Discovery* Early Warning System only in 2021 [8,10]. Interestingly, nitazene drugs have already appeared in the Brazilian territory, despite opioids not being very popular in the country in the last decades [7]. However, after July 2022, a consistent increase in the numbers of nitazene seizures, particularly metonitazene, in contrast to other opioids in the same period, or even before, has intrigued police officers and related professionals. New psychoactive substances continue to be considered a global phenomenon due to the threats that they pose. However, the drug profile in each territory or country can influence the flow of these substances in other countries [2].

Therefore, the constant monitoring of such trends is necessary, especially considering that Brazil has continental dimensions and has not been seen as an important NPS market route in the world. In addition, the fact that Brazil does not have a high consumption of opioids, whether legal or illegal, is what stands out the most when the occurrence of synthetic opioids in many police seizures is now reported. Thus, this article describes the unprecedented seizure data of synthetic opioids in Brazil from July 2022 to April 2023.

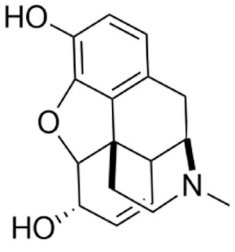
2. Methodology

Herbal fragments and pills samples were seized from July 2022 to April 2023 by the São Paulo State Police. Samples were prepared according to the procedure described by De Araujo et al., 2023 [11]. Briefly, approximately 40 mg were collected from each case and dissolved in 2 mL of methanol in Falcon tubes and subjected to agitation for 15 minutes at 30°C. All the samples were identified in the Laboratory of

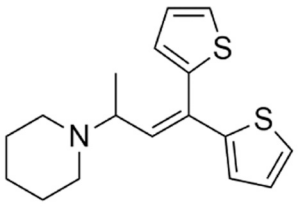


Core structure of nitazenes

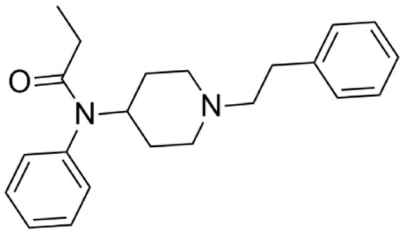
	R1	R2	R3	R4
Metonitazene	NO_2	OCH_3	CH_2CH_3	CH_2CH_3
Etonitazene	NO_2	OCH_2CH_3	CH_2CH_3	CH_2CH_3
Protonitazene	NO_2	$OCH_2CH_2CH_3$	CH_2CH_3	CH_2CH_3
Butonitazene	NO_2	$OCH_2CH_2CH_2CH_3$	CH_2CH_3	CH_2CH_3
Isonitazene	NO_2	$OCH(CH_3)_2$	CH_2CH_3	CH_2CH_3



Morphine



Piperidylthiambutene



Fentanyl

Fig. 1. Illustration of the chemical structures of opioids. Morphine, piperidylthiambutene, and fentanyl were included as comparison to the nitazene group.

Forensic Chemistry by gas chromatography–mass spectrometry (GC–MS) - using SWGDRUG and CAYMAN libraries - liquid chromatography–high-resolution mass spectrometry (LC–QTOF-MS) or nuclear magnetic resonance (NMR), according to the laboratory standard operational procedures and the Scientific Working Group for the Analysis of Seized Drugs (SWGDRUG) recommendations.

3. Results

From July 2022 to April 2023, a total of 140 samples seized by the Police contained an opioid, either isolated or mixed with another substance. Of these cases, 133 (95 %) contained a nitazene, while only 5 % involved non-nitazene opioids (Fig. 2). Curiously, classic opioids and fentanyl were not found mixed with new synthetic opioids in the same drug sample. The percentage of isolated and mixed compounds in both groups were different for each group. Nitazenes were found isolated in 28.6 % and mixed in 71.4 % of the samples, while non-nitazenes were found in 27.1 % and mixed in 72.9 % of the samples (Fig. 2).

In the samples containing a substance of the nitazene group, metonitazene was the most frequent drug seized, appearing in 125 (72 %) of the cases. Of those, metonitazene was found as the only opioid in 36 cases (20 %), being the only nitazene found isolated. In the other 89 cases, nitazenes were found associated with other drugs, of which the synthetic cannabinoids were the most prevalent, especially MDMB-4en-PINACA. On the other hand, only 7 of the 140 (5 %) seizures in the timeframe of this study contained a non-nitazene opioid (morphine and fentanyl only). Curiously, these opioids were found mixed with other substances in the same percentage of the nitazene group, however, the number of cases is too low to draw proper conclusions. Interestingly, this group of non-nitazene opioids was also found associated with cannabinoids, similar to the nitazene group. Therefore, synthetic cannabinoids are the most prevalent substances associated with nitazene and non-nitazene opioids, followed by some stimulants, such as amphetamines. For the most of the detected drugs, gas chromatography-mass spectrometry (GC-MS) was the technique used for identification, comparing with libraries and standards of reference. Nitazenes were identified using liquid chromatography–high-resolution mass spectrometry (LC–QTOF-MS) and nuclear magnetic resonance (NMR). All the substances detected in the samples can be found in Table 1 (Supplementary material)

4. Discussion

Based on the data provided by the São Paulo State Police in Brazil, it is evident that the opioid scenario in the country has changed from previous years. This paradigm shift is noticeable when evaluating the profile of the general seizures made by the STSP-NCC in São Paulo, responsible for processing all cases related to the capital of São Paulo, the most populous region of the country, with more than 19 million inhabitants. During the year 2022, for example, cases involving classic drugs were reported, such as marijuana with 5687 and cocaine with 6451 items, being a very expressive number when compared to other regions, presenting as synthetic drugs and NPS amphetamines with 837 items, synthetic cannabinoids with 898, and synthetic opioids only with 30, a number much lower than the other drugs. These data refer to the observation of the same data survey from which the information presented here was taken.

Interestingly, all cases containing nitazenes were found in herbal matrices, where the police expected to find synthetic cannabinoids, [11], benzodiazepines, and even cocaine [12], due to this presentation being intended to be smoked. No comprehensive pharmacological or toxicological studies are available regarding this form of intake for opioids. This type of matrix was responsible for 99 % of cases containing both nitazenes and non-nitazene opioids in the state of São Paulo within the timeframe of this study. As far as we know, it is the first report in which these synthetic opioids were detected in the form of herbal fragments. The effect of smoking a potent opioid together with synthetic cannabinoids is unpredictable and most users cannot be aware of what they are using.

Another observation worth pointing out is that in almost all cases, the nitazenes seized by the Police were mixed with synthetic cannabinoids, especially ADB-BUTINACA and MDMB-4en-PINACA. Nevertheless, these synthetic cannabinoids in particularly were not chosen aleatory, these types of synthetic cannabinoids are commonly found in seized drugs in other countries, such as the USA, being MDMB-4en-PINACA and ADB-BUTINACA responsible for 31.41 % and 22.78 % of synthetic cannabinoids reports in the United States, between January and June 2022, respectively, showing this might be an international trend in this type of synthetic cannabinoids [13]. In addition, according to Ti *et al.* in a study analyzing drug adulteration that was being sold as opioids in Vancouver and Toronto, 3 % of them were mixed with some

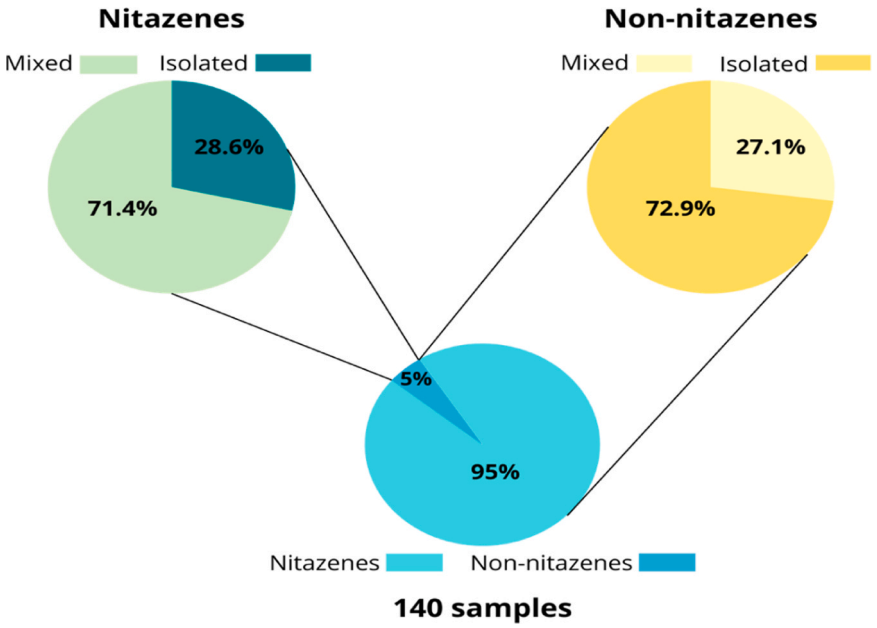


Fig. 2. Overview of the opioid-containing materials seized in Brazil from July 2022 to April 2023.

Table 1
Detailed description of the substances found in the samples containing more than one drug. The nitazene section is organized according to metonitazene-containing samples, as it was the most frequently detected compound. THC- tetrahydrocannabinol; MDA- 3,4-methylenedioxyamphetamine; MDMA- 3,4-methylenedioxymethamphetamine. (Supplementary material).

Case	Detected substances					City	Matrix
1	BUTONITAZENE	BZO-HEXOXIZID	ADB-FUBIATA	ADB-5Br-INACA	METONITAZENE	FRANCO DA ROCHA	HERBAL FRAGMENTS
2	BZO-HEXOXIZID	ADB-FUBIATA	COCAINE	METONITAZENE		SÃO PAULO	HERBAL FRAGMENTS
3	BZO-HEXOXIZID	BZO-4en-POXIZID	MDMB-5Br-INACA	THC	PROTONITAZENE	CAJAMAR	HERBAL FRAGMENTS
4	MDMB-5Br-INACA	METONITAZENE	COCAINE	THC	BZO-4en-POXIZID	FRANCISCO MORATO	HERBAL FRAGMENTS
5	MDMB-BUTINACA	ADB-BUTINACA	ADB-PINACA	BZO-HEXOXIZID	METONITAZENE	SÃO PAULO	HERBAL FRAGMENTS
6	BZO-HEXOXIZID	4F-MDMB-BICA	MDMB-BUTINACA	ADB-BINACA	METONITAZENE	SÃO PAULO	HERBAL FRAGMENTS
7	METONITAZENE					SÃO PAULO	HERBAL FRAGMENTS
8	METONITAZENE	MDMB-4en-PINACA	ADB-5Br-BUTINACA	COCAINE		SÃO PAULO	HERBAL FRAGMENTS
9	MDMB-4en-PINACA	METONITAZENE	COCAINE			SÃO PAULO	HERBAL FRAGMENTS
10	METONITAZENE					SÃO PAULO	HERBAL FRAGMENTS
11	ADB-FUBIATA	BZO-HEXOXIZID	BUTONITAZENE	COCAINE		CAIEIRAS	HERBAL FRAGMENTS
12	ADB-5Br-INACA	METONITAZENE				DIADEMA	HERBAL FRAGMENTS
13	ADB-5Br-INACA	BZO-4en-POXIZID	METONITAZENE	BUTONITAZENE		DIADEMA	HERBAL FRAGMENTS
14	ADB-FUBIATA	BZO-HEXOXIZID	BUTONITAZENE			MAIRIPORÃ	HERBAL FRAGMENTS
15	METONITAZENE					DIADEMA	HERBAL FRAGMENTS
16	METONITAZENE					SÃO BERNARDO DO CAMPO	HERBAL FRAGMENTS
17	METONITAZENE					SÃO PAULO	HERBAL FRAGMENTS
18	METONITAZENE					SÃO PAULO	HERBAL FRAGMENTS
19	METONITAZENE					SÃO PAULO	HERBAL FRAGMENTS
20	METONITAZENE	ADB-5Br-BINACA				SUMARÉ	HERBAL FRAGMENTS
21	METONITAZENE	MDMB-4en-PINACA	ADB-4en-PINACA			SÃO PAULO	HERBAL FRAGMENTS
22	MDMB-4en-PINACA	ADB-BINACA	METONITAZENE			SÃO PAULO	HERBAL FRAGMENTS
23	METONITAZENE					GUARULHOS	HERBAL FRAGMENTS
24	ADB-5BR-BINACA	METONITAZENE				SÃO PAULO	HERBAL FRAGMENTS
25	METONITAZENE	MDMB-4en-PINACA				SÃO PAULO	HERBAL FRAGMENTS
26	BZO-HEXOXIZID	BZO-4EN-POXIZID	ADB-FUBIATA	BUTONITAZENE	COCAINE	SÃO PAULO	HERBAL FRAGMENTS
27	METONITAZENE	COCAINE				CARAPICUÍBA	HERBAL FRAGMENTS
28	METONITAZENE	THC	COCAINE			RIBEIRÃO PIRES	HERBAL FRAGMENTS
29	METONITAZENE	ADB-5Br-INACA	ADB-BINACA			DIADEMA	HERBAL FRAGMENTS
30	METONITAZENE	BZO-4en-POXIZID	ADB-5r-INACA	THC		DIADEMA	HERBAL FRAGMENTS
31	METONITAZENE	ADB-5Br-INACA	BZO-4en-POXIZID			DIADEMA	HERBAL FRAGMENTS
32	METONITAZENE	MDMB-4en-PINACA	ADB-BINACA			SÃO PAULO	HERBAL FRAGMENTS
33	MDMB-4en-PINACA	ADB-BINACA	BUTONITAZENE	COCAINE		SÃO BERNARDO DO CAMPO	HERBAL FRAGMENTS
34	METONITAZENE	MDMB-4en-PINACA				BIRITIBA MIRIM	HERBAL FRAGMENTS
35	METONITAZENE					GUARULHOS	HERBAL FRAGMENTS
36	FENTANYL					SÃO PAULO	POWDER

(*continued on next page*)

Table 1 (*continued*)

Case	Detected substances					City	Matrix
37	METONITAZENE					SÃO PAULO	HERBAL FRAGMENTS
38	METONITAZENE					SÃO PAULO	HERBAL FRAGMENTS
39	METONITAZENE					SÃO PAULO	HERBAL FRAGMENTS
40	METONITAZENE					SÃO PAULO	HERBAL FRAGMENTS
41	MDMB-4en-PINACA	METONITAZENE				DIADEMA	HERBAL FRAGMENTS
42	METHAMPHETAMINE	MDMA	BUTONITAZENE			GUARULHOS	PILLS
43	MDMB-4en-PINACA	BUTONITAZENE				SÃO PAULO	HERBAL FRAGMENTS
44	MORPHINE					SÃO PAULO	PILLS
45	MORPHINE					SÃO PAULO	PILLS
46	ADB-BUTINACA	METONITAZENE				SÃO PAULO	HERBAL FRAGMENTS
47	5F-ADB	MDMB-4en-PINACA	METONITAZENE	BROMAZOLAM	ADB-BUTINACA	SÃO PAULO	HERBAL FRAGMENTS
48	MDMB-4en-PINACA	ADB-BINACA	COCAINE	FENTANYL		SÃO PAULO	HERBAL FRAGMENTS
49	MDMB-4en-PINACA	METONITAZENE	BUTONITAZENE	ADB-4en-PINA		SÃO PAULO	HERBAL FRAGMENTS
50	ADB-BUTINACA	MDMB-4en-PINACA	4F-MDMB-BICA	ADB-5Br-INACA	METONITAZENE	SÃO PAULO	HERBAL FRAGMENTS
51	METONITAZENE	ADB-5Br-INACA				MIRANDÓPOLIS	HERBAL FRAGMENTS
52	MDMB-4en-PINACA	BUTONITAZENE	METONITAZENE	ADB-4EN-PINACA		SÃO PAULO	HERBAL FRAGMENTS
53	MDMB-4en-PINACA	METONITAZENE				SÃO PAULO	HERBAL FRAGMENTS
54	FENTANYL					SÃO PAULO	HERBAL FRAGMENTS
55	BROMAZOLAM	ADB-BINACA	METONITAZENE			SÃO PAULO	HERBAL FRAGMENTS
56	MDMB-4en-PINACA	5F-ADB	METONITAZENE			SÃO PAULO	HERBAL FRAGMENTS
57	METONITAZENE					SÃO PAULO	HERBAL FRAGMENTS
58	METONITAZENE					SÃO PAULO	HERBAL FRAGMENTS
59	ADB-BUTINACA	METONITAZENE				SÃO PAULO	HERBAL FRAGMENTS
60	METONITAZENE	ADB-BUTINACA				GUARULHOS	HERBAL FRAGMENTS
61	METONITAZENE	BROMAZOLAM				SÃO PAULO	HERBAL FRAGMENTS
62	MDMB-4en-PINACA	ADB-BUTINACA	METONITAZENE			ITANHAÉM	HERBAL FRAGMENTS
63	METONITAZENE					SANTOS	HERBAL FRAGMENTS
64	METONITAZENE	ADB-BUTINACA				SÃO PAULO	HERBAL FRAGMENTS
65	METONITAZENE	ADB-BUTINACA				SÃO PAULO	HERBAL FRAGMENTS
66	5F-ADB	MDMB-4en-PINACA	ADB-BINACA	METONITAZENE		SÃO PAULO	HERBAL FRAGMENTS
67	METONITAZENE					SÃO PAULO	HERBAL FRAGMENTS
68	METONITAZENE	ADB-BINACA	THC			SÃO PAULO	HERBAL FRAGMENTS
69	METONITAZENE	ADB-BUTINACA	THC			SÃO PAULO	HERBAL FRAGMENTS
70	METONITAZENE					SÃO PAULO	HERBAL FRAGMENTS
71	MDMB-4en-PINACA	METONITAZENE				SÃO PAULO	HERBAL FRAGMENTS
72	FENTANYL	THC				SÃO PAULO	HERBAL FRAGMENTS
73	FENTANYL					SÃO PAULO	HERBAL FRAGMENTS
74	ADB-BUTINACA	METONITAZENE				SÃO PAULO	HERBAL FRAGMENTS
75	ADB-BUTINACA	METONITAZENE				SÃO PAULO	HERBAL FRAGMENTS

(*continued on next page*)

Table 1 (*continued*)

Case	Detected substances					City	Matrix
76	MDMB-BUTINACA	METONITAZENE				SÃO PAULO	HERBAL FRAGMENTS
77	METONITAZENE	ADB-BUTINACA	XYLAZINE			SÃO PAULO	HERBAL FRAGMENTS
78	METONITAZENE					SÃO PAULO	HERBAL FRAGMENTS
79	MDMB-4en-PINACA	METONITAZENE	ADB-4EN-PINACA	THC		SÃO PAULO	HERBAL FRAGMENTS
80	MDMB-4en-PINACA	METONITAZENE				SÃO PAULO	HERBAL FRAGMENTS
81	METONITAZENE	ADB-BINACA	MDMB-BUTINACA			GUARULHOS	HERBAL FRAGMENTS
82	METONITAZENE	MDMB-4en-PINACA	ADB-BINACA	BROMAZOLAM		GUARULHOS	HERBAL FRAGMENTS
83	METONITAZENE					SÃO PAULO	HERBAL FRAGMENTS
84	METONITAZENE	MDMB-4en-PINACA	MDMB-BUTINACA	ADB-4en-PINACA	XYLAZINE	SÃO PAULO	HERBAL FRAGMENTS
85	METONITAZENE					SÃO PAULO	HERBAL FRAGMENTS
86	ADB-BUTINACA	BROMAZOLAM	THC	MDMB-5Br-INACA	METONITAZENE	MIRANDÓPOLIS	HERBAL FRAGMENTS
87	METONITAZENE					PRAIA GRANDE	HERBAL FRAGMENTS
88	METONITAZENE					PRAIA GRANDE	HERBAL FRAGMENTS
89	MDMB-4en-PINACA	METONITAZENE				PRAIA GRANDE	HERBAL FRAGMENTS
90	MDMB-BUTINACA	METONITAZENE	MDMB-4en-PINACA			SÃO PAULO	HERBAL FRAGMENTS
91	MDMB-BUTINACA	METONITAZENE	MDMB-4en-PINACA			SÃO PAULO	HERBAL FRAGMENTS
92	ADB-BUTINACA	METONITAZENE	MDA			PRAIA GRANDE	HERBAL FRAGMENTS
93	ADB-BUTINACA	METONITAZENE				SANTOS	HERBAL FRAGMENTS
94	METONITAZENE					MONGAGUÁ	HERBAL FRAGMENTS
95	METONITAZENE					MONGAGUÁ	HERBAL FRAGMENTS
96	MDMB-4en-PINACA	MDMB-BUTINACA	METONITAZENE			SÃO PAULO	HERBAL FRAGMENTS
97	MDMB-4en-PINACA	MDMB-BUTINACA	METONITAZENE			SÃO PAULO	HERBAL FRAGMENTS
98	ADB-BUTINACA	5F-ADB	METONITAZENE			GUARULHOS	HERBAL FRAGMENTS
99	ADB-BUTINACA	MDMB-BUTINACA	MDMB-4en-PINACA	METONITAZENE		SÃO PAULO	HERBAL FRAGMENTS
100	MDMB-4en-PINACA	METONITAZENE				SÃO PAULO	HERBAL FRAGMENTS
101	METONITAZENE	5F-ADB	COCAINE	MDMB-4en-PINACA	PROTONITAZENE	SÃO PAULO	HERBAL FRAGMENTS
102	ADB-BUTINACA	METONITAZENE				SÃO PAULO	HERBAL FRAGMENTS
103	MDMB-5BR-INACA	ADB-BUTINACA	METONITAZENE	MDMB-4en-PINACA	THC	SÃO PAULO	HERBAL FRAGMENTS
104	ADB-BUTINACA	BROMAZOLAM	MDMB-4en-PINACA	MDMB-5Br-INACA	METONITAZENE	SÃO PAULO	HERBAL FRAGMENTS
105	MDMB-BUTINACA	5F-ADB	ADB-PINACA	METONITAZENE		SÃO PAULO	HERBAL FRAGMENTS
106	MDMB-BUTINACA	5F-ADB	ADB-PINACA	METONITAZENE		SÃO PAULO	HERBAL FRAGMENTS
107	ADB-BUTINACA	METONITAZENE				SÃO PAULO	HERBAL FRAGMENTS
108	MDMB-4en-PINACA	METONITAZENE				SÃO PAULO	HERBAL FRAGMENTS
109	METONITAZENE	ADB-BINACA				SÃO VICENTE	HERBAL FRAGMENTS
110	MDMB-4en-PINACA	ADB-BUTINACA	METONITAZENE			SÃO VICENTE	HERBAL FRAGMENTS
111	MDMB-4en-PINACA	MDMB-BUTINACA	ISONITAZENE			SÃO PAULO	HERBAL FRAGMENTS
112	5F-ADB	MDMB-BUTINACA	ADB-PINACA	MDMB-4en-PINACA	METONITAZENE	SÃO PAULO	HERBAL FRAGMENTS
113	5F-ADB	MDMB-BUTINACA	ADB-PINACA	MDMB-4en-PINACA	METONITAZENE	SÃO PAULO	HERBAL FRAGMENTS

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Table 1 (*continued*)

Case	Detected substances				City	Matrix
114	METONITAZENE				SÃO PAULO	HERBAL FRAGMENTS
115	METONITAZENE				SÃO PAULO	HERBAL FRAGMENTS
116	METONITAZENE				SÃO PAULO	HERBAL FRAGMENTS
117	METONITAZENE				SÃO PAULO	HERBAL FRAGMENTS
118	METONITAZENE	XYLAZINE	ADB-BINACA		SÃO PAULO	HERBAL FRAGMENTS
119	METONITAZENE	XYLAZINE	ADB-BINACA		SÃO PAULO	HERBAL FRAGMENTS
120	METONITAZENE				SÃO PAULO	HERBAL FRAGMENTS
121	METONITAZENE				SÃO PAULO	HERBAL FRAGMENTS
122	METONITAZENE				SÃO PAULO	HERBAL FRAGMENTS
123	METONITAZENE				SÃO PAULO	HERBAL FRAGMENTS
124	ADB-BUTINACA	METONITAZENE			SÃO PAULO	HERBAL FRAGMENTS
125	5F-ADB	ADB-BUTINACA	METONITAZENE		MONGAGUÁ	HERBAL FRAGMENTS
126	MDMB-4en-PINACA	METONITAZENE	5F-ADB		PRAIA GRANDE	HERBAL FRAGMENTS
127	METONITAZENE				PRAIA GRANDE	HERBAL FRAGMENTS
128	METONITAZENE	BZO-HEXOXIZID	ADB-BUTINACA		MONGAGUÁ	HERBAL FRAGMENTS
129	METONITAZENE	BZO-HEXOXIZID			MONGAGUÁ	HERBAL FRAGMENTS
130	METONITAZENE	ADB-BUTINACA			SÃO VICENTE	HERBAL FRAGMENTS
131	METONITAZENE	ADB-BUTINACA			SÃO VICENTE	HERBAL FRAGMENTS
132	ADB-BUTINACA	METONITAZENE	COCAINE		PRAIA GRANDE	HERBAL FRAGMENTS
133	METONITAZENE	ADB-BUTINACA	COCAINE		PRAIA GRANDE	HERBAL FRAGMENTS
134	METONITAZENE	XYLAZINE			PRAIA GRANDE	HERBAL FRAGMENTS
135	METONITAZENE	XYLAZINE			PRAIA GRANDE	HERBAL FRAGMENTS
136	MDMB-4en-PINACA	ADB-BUTINACA	5F-ADB	METONITAZENE	SÃO PAULO	HERBAL FRAGMENTS
137	MDMB-4en-PINACA	ADB-BINACA	5F-ADB	METONITAZENE	SÃO PAULO	HERBAL FRAGMENTS
138	METONITAZENE				SÃO PAULO	HERBAL FRAGMENTS
139	METONITAZENE				SÃO PAULO	HERBAL FRAGMENTS
140	METONITAZENE	COCAINE				

synthetic cannabinoid but none contained nitazenes [14]. In addition to these mixtures, in some cases a veterinarian anesthetic, xylazine, was detected mixed with metonitazene and synthetic cannabinoids (ADB--BUTINACA, MDMB-4en-PINACA). This type of combination was never reported in Latin American countries.

The combination of these two different classes of substances is curious. According to recent studies, cannabinoid receptor agonists, when combined with morphine, can exert synergistic or increased analgesic effects, serving to reduce opioid doses and consequently reduce side effects and dependence [15–18]. Additionally, the receptors of both pharmacological classes are coupled to similar intracellular signaling mechanisms, leading to synergistic effects when combined. In addition, there is evidence that cannabinoids, whether synthetic or of natural origin, can increase the synthesis and/or release of endogenous opioids [19]. As a consequence, a plausible hypothesis is that these mixtures are being deliberately produced. Ti *et al.*, have hypothesized that synthetic cannabinoids may be purposefully added to opioids given that they can produce a similar high that many opioid users seek, at a fraction of the cost. However, the association of these different classes of drugs has the potential to result in worse and unpredictable health outcomes, particularly for those inadvertently taking these mixtures [14]. Cannabinoids and opioids share similar pharmacological effects, including analgesia, sedation, hypothermia, inhibition of motor activity, hypotension, and sedation, but the analgesic benefits/disadvantages of cannabinoids and opioids combined have not been fully explored. Thus, unlike naloxone for opioids, there is no specific antidote clinically approved to reverse the effects of synthetic cannabinoids, making individuals more vulnerable to overdoses [20]. A final remark worth mentioning is that almost simultaneously with the seizures of nitazenes, a consistent number of reports on “K4, zombie drug, K drugs or super marijuana” raises questions about the content of these drugs. [21]. It could be caused by the association with other psychoactive drugs, such as these novel opioids, although this hypothesis needs further evidence.

The low numbers of opioid abuse in Brazil can be associated with several reasons. For example, the highly restrictive legislation that takes place in Brazil does not allow easy access to opioid-based medications

for the general population or even health professionals. In that case, physicians need a valid registration in the competent organ to be authorized to prescribe opioids and are encouraged to do so only when extremely necessary. Thus, patients are mainly treated with non-opioid medications, such as acetaminophen, acetylsalicylic acid, pyrazolone derivatives (dipyrone), and other non-steroidal anti-inflammatory drugs, while opioids are prescribed for the treatment of severe pain or in terminal cases, such as cancer. In fact, opioids account for less than 2 % of these drugs prescribed to treat pain and are represented by codeine and tramadol, which are mild MOR agonists [22]. The association of these factors in addition to the fear of an opioid crisis has prevented the major abuse of this class of drugs by the Brazilian population up until now.

5. Conclusion

It seems that opioids have been unprecedentedly becoming more relevant in Brazilian territory. Although a definitive explanation for that is still missing, it could be attributed to different causes, such as the profile of users, facilitated access, legislation, sociocultural issues as well as the emergence of NPS phenomenon worldwide. In fact, the high cases of synthetic cannabinoids and stimulants, often combined with more than one drug and with an extremely high potency, are more concerning threats to Brazilian standards in the present day. However, much remains to be done to understand the consequences of the results provided in the present article. There are relatively few seizures of opioids when compared to the other drugs seized in the country but both law enforcement and health professionals need to remain vigilant, as the threat posed by these new compounds begins to expand in the Brazilian territory.

Ethics declaration

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

José Luiz Costa: Writing – review & editing, Visualization, Supervision, Conceptualization. **Alexandre Learth Soares:** Resources, Project administration, Investigation, Formal analysis, Data curation. **Mauricio Yonamine:** Writing – review & editing, Visualization, Validation, Supervision, Conceptualization. **André Luis Fabris:** Writing – review & editing, Supervision, Investigation. **Karen Rafaela Gonçalves de Araujo:** Writing – original draft, Investigation, Formal analysis, Data curation. **Luiz Ferreira Neves Júnior:** Supervision, Resources, Methodology.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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