

ANALYTICALLY CONFIRMED PRESENCE OF PSYCHOACTIVE SUBSTANCES, ESPECIALLY NEW PSYCHOACTIVE SUBSTANCES IN A GROUP OF PATIENTS HOSPITALIZED WITH MENTAL AND BEHAVIOURAL DISORDERS DUE TO THE USE OF PSYCHOACTIVE SUBSTANCES DIAGNOSIS

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Abstract

Objectives: The study assessed the presence of new psychoactive substances (NPS) in comparison to “classic” drugs in the group of newly admitted patients with mental and behavioral disorders due to the use of psychoactive substances diagnosis (section F11–19 according to ICD-10). **Material and Methods:** Data from anamnesis and the blood and urine samples were collected from 116 patients diagnosed with mental and behavioral disorders due to psychoactive substance use. All of them expressed written informed consent. Analytical confirmation was obtained by high-performance liquid chromatography coupled to tandem mass spectrometry (LC/MS/MS). Liquid-liquid extraction was used for sample preparation. **Results:** In the sample, 108 (93%) of 116 were positive for psychoactive substances (including 96 cases where >1 substance was found), 69% of individuals were tested positive for opioids and 67% for benzodiazepines. Eleven (9%) of 116 patient samples were positive for NPS. We detected 7 different substances. Six of them were synthetic cannabinoids: PB-22, MDMB-CHMICA, MMB-CHMICA, AB-CHMINACA, MMB-FUBINACA, THJ-2201 and one synthetic cathinone 3-CMC. **Conclusions:** The prevalence and NPS profile (the predominance of synthetic cannabinoids) are similar in the group of people with addiction to psychoactive substances as in populations of people taking recreational drugs and the overdose patients admitted to the hospital. *Int J Occup Med Environ Health.* 2022;35(4):485–95

Key words:

THC, epidemiology, addiction, new psychoactive substances, opioids, amphetamine

Funding: this research was supported by Faculty of Medicine, University of Warmia and Mazury, Olsztyn, Poland (grant No. 25.610.001-300 entitled “Monitoring the prevalence of psychoactive substances in the population of Warmińsko-Mazurskie Voivodeship residents,” grant manager: Piotr Engelgardt). The funding source played no role in the study design, in the analysis and interpretation the data, in the writing of the report or in the decision to submit the paper for publication.

Received: April 28, 2021. Accepted: February 2, 2022.

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INTRODUCTION

It is estimated that over 96 million adults or, according to other statistics, almost a quarter of the adult population in the European Union have tried illegal substances during their lifespan [1].

The most commonly used drugs are cannabis, cocaine, amphetamine (AMF) and 3,4-methylenedioxy-methamphetamine (MDMA). However, the frequency of use for each drug varies considerably from country to country depending on the age of users [1,2].

It is estimated that 26.3% of adult Europeans (15–64 years) have had contact with cannabis in their lifetime [1].

Over the last years, environmental signals from both formal and informal research and monitoring sources have been showing critical recent developments within Europe's new psychoactive substances (NPS) market [1]. New psychoactive substances are a heterogeneous class of typically synthetic molecules including: synthetic cannabinoid receptor agonists, synthetic cathinones, amphetamine-derivatives, psychedelic phenethylamines, ketamine derivatives, novel tryptamines, synthetic opioids and sedatives (GABA-A/B agonists) [3–5]. The NPS are cheap and easily available either on the street or from websites [4–8]. In Poland, NPS are usually known under the name of “boosters”.

Synthetic cannabinoid receptor agonists have been the most popular NPS in recent years. According to the current observations, they are especially popular among high-risk drug-using populations. Such groups include prisoners from approx. 2/3 (N = 19) of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) reporting countries: Belgium, Bulgaria, Croatia, the Czech Republic, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Poland, Portugal, Romania, Slovenia, Sweden, Turkey and the United Kingdom [1].

The majority of research studying NPS uses questionnaires [6–11] or analyses of medical data [12,13] and concerns either recreational use or cases of acute intoxication [14].

There are many surveys available in the literature (in which data are collected during an anamnesis) describing the profile of people taking NPS in various social groups [7–13]. Such studies were conducted also on patients in psychiatric hospitals [12,13].

There are fewer studies in which the use of NPS has been confirmed by analytical methods, these studies most often relate to acute cases of intoxication in people taking these substances as recreational drugs [14–18].

Currently, there is limited literature on the socio-demographic profile of NPS consumers.

Those studies have shown that young males, abusing other (non-NPS) drugs, especially after combining some of them, are more likely to use NPS [7–16]. According to some reports, NPS users have a higher possibility of displaying risky behavior [10,11,19]. Experienced individuals with substance use disorder add NPS to typically used, illicit substances [7,19].

The group of NPS-only users is very rare. Sutherland et al. [10] found that only 5.7% of NPS users and 0.07% of the cohort group did not use drugs other than NPS.

The prevalence of NPS in the population of individuals with an addiction, often taking psychoactive substances, is poorly estimated [11]. There has been previously published a study of a similar patient cohort analyzed using the anamnesis only. In this study, 34% of the patients reported taking NPS in the past, without indicating the particular time of intake and substance type [20].

The goal of our study was to check the presence of NPS in comparison to “classic” drugs in blood and urine of the group of newly admitted patients with mental and behavioral disorders due to the use of psychoactive substances diagnosis (section F11–19 according to ICD-10).

MATERIAL AND METHODS

A cross-sectional study at the Regional Psychiatric Hospital in Olsztyn, Poland, was performed to estimate the analytically confirmed prevalence of NPS in com-

parison to “classic” drugs in the population of a newly admitted patients group with mental and behavioral disorders due to psychoactive substance abuse (F11–19 section).

A group of adult patients (18–79 years old) diagnosed as individuals with substance use disorder (F11–19 according to the ICD-10) was admitted to the Regional Psychiatric Hospital in Olsztyn, Poland between September 1, 2016 and September 30, 2017. They were informed about the possibility of joining the study. After obtaining informed written consent from patients, blood and urine samples were collected.

For patients whose mental state allowed for informed consent, written consent was obtained during the examination after admission to the hospital. In such cases, samples of biological material (blood and urine) were taken after the medical examination. There were also patients who were mentally incapable of giving consent to take part in the study. In such cases, the samples of blood were taken during the blood collection for diagnostic tests. When their mental condition improved enough for them to give the written consent, their urine samples were collected. If patients refused consent, their samples were destroyed, and they were excluded from the study.

Additionally, the following data were collected from the patients’ medical records: age, sex, type of admission to the hospital (emergency, elective), data on substances taken within 48 h preceding the admission to the hospital, comorbid diseases and other symptoms.

Samples of biological materials and data obtained from medical records were anonymized and marked with a unique study code.

This survey was approved by the local Bioethics Committee of the University of Warmia and Mazury in Olsztyn. Data were placed into an Excel spreadsheet using a coded ID number which could not be used to identify individual patients retrospectively. The spreadsheet was protected

by a password and stored on the university servers only. The password was available only to the authors of this survey.

Laboratory analysis of samples

Since standard “classic” drugs are marked in both blood and urine, the authors also decided to analyze urine for the NPS in this survey.

The validated LC-MS/MS method was used for the blood and urine samples analysis in the conditions described below:

- Sample preparation: Liquid-liquid extraction in the mode called simplified liquid-liquid extraction was used for sample preparation. Before extraction, deuterated internal standards were added to all samples.
- Sample analysis: High-performance liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) method was used for sample analysis. Reverse phase liquid chromatography was used for chromatographic separation. Mass spectrometry detection was used with electrospray ionization in the positive mode. Multiple reaction measurement was used for the final measurement of each monitored compound.

This analytical screening covered 36 substances including both legal and illegal drugs. These included mainly classic drugs like AMF, cannabis, opioids, benzodiazepines (BDZ) and cocaine – listed in detail in Table 1.

Statistical analysis

The Fisher’s exact test was used to show the differences in sex distribution between the tested groups. It was conducted due to the prevalence in expected values. The Welch test was utilized to compare the age of the patients from these groups (with NPS and without NPS) [21]. The reason for performing such analysis was the heterogeneous variances between the groups (the variance in the NPS-negative group was 229.8, while the variance in the NPS-positive group was 30.66).

Table 1. Substances covered by analytical screening in the study on 116 patients diagnosed with mental and behavioral disorders due to psychoactive substance use, Olsztyn, Poland

Substance	
Benzylpiperazine	Oxazepam
Morphine	Lorazepam
Methamphetamine	Temazepam
Amphetamine	Diazepam
MDMA	Diclazepam
3-CMC	MMB-FUBINACA
Mexedrone	AB-CHMINACA
Eutylone	5F-ADB
Benzoylcegonine	PB-22
Cocaine	XLR-11
3,4-DMMC	THJ-2201
Zolpidem	MMB-CHMICA
Tramadol	NM-2201
Fu-F	JWH-018
Nitrazepam	MDMB-CHMICA
Clonazepam	5F-APINACA
Flunitrazepam	UR-144
Alprazolam	THC

3,4-DMMC – 3,4-dimethylmethcathinon; 3-CMC – 3-chloromethcathinone; Fu-F – furanyl-fentanyl; JWH-018 – 1-pentyl-3-(1-naphthoyl)indole; MDMA – 3,4-methylenedioxy-methamphetamine; THC – tetrahydrocannabinol.

RESULTS

There were 4094 patients admitted to the hospital during the study period, of which 196 were patients diagnosed with mental and behavioral disorders due to psychoactive substance use (section F11–19 of ICD-10). In total, 116 patients expressed written informed consent for the study.

Table 2 presents the demographic data of the examined group. The average age was 33.6 years, the youngest patient was 18 years old and the oldest was 79 years old.

Elective admissions concerned patients admitted to the Withdrawal Syndrome Treatment Unit. It is a department specializing in alcohol withdrawal syndrome including complications such as delirium or epileptic sei-

Table 2. Demographic characteristic of patients in the study on mental and behavioral disorders due to psychoactive substance use, Olsztyn, Poland

Variable	Participants (N = 116)	
	n	%
Sex		
male	91	78
female	25	22
Age		
≤20 years	7	6
21–30 years	54	47
31–40 years	35	30
>40 years	20	17
Admission to hospital type		
emergency admission	67	58
elective admission	49	42

zures, treatment of other alcohol psychoses, consciousness disorders and non-psychotic psychiatric disorders, detoxification. It also provides initiation of therapy for patients legally forced into rehab treatment and conducts clinic observation oriented to a forensic and psychiatric issue opinion.

Emergency admissions concerned patients presenting with the symptoms of mental disorders. Patients with acute life-threatening symptoms of intoxication are initially treated in the emergency ward and then transferred to appropriate departments depending on their specific health problem and overall condition (intensive care unit, toxicology department or others).

In the study group of 116 people, patients were found as described below:

- 14 people were diagnosed with section F11 (opioid-related disorders);
- 8 people were diagnosed with section F13 (sedative, hypnotic, or anxiolytic related disorders);
- 14 people were diagnosed with section F15 (other stimulant related disorders);

– 90 people were diagnosed with section F19 (other psychoactive substance-related disorders).

In 12 cases, accompanying psychiatric conditions were found in addition to those classified as F11–19. These were diseases representing the following groups:

- mood disorders F30–39 (4 cases);
- anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders F40–48 (1 case);
- mental disorders due to known physiological conditions F01–09 (3 cases);
- schizophrenia F20 (2 cases);
- disorders of adult personality and behavior F60–69 (1 case).

What is more, 2 people were diagnosed with comorbid alcohol related disorders – F10 according to the ICD-10.

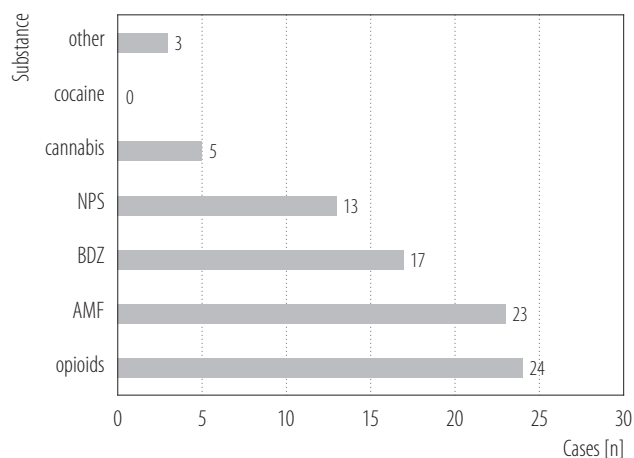
Analysis of patients' medical records

For the purpose of this study, the authors arbitrarily decided to include data from the anamnesis regarding psychoactive substances that have been taken in the last 48 h.

Forty-six patients denied using any illicit substances, 55 patients gave information about the intake of one psychoactive substance, and 15 patients reported taking >1 substance.

In Poland, NPS are commonly referred to as “boosters,” which explains why only 2 subjects were able to give the proper name of the substance used (mephedrone). That is the reason the NPS group was treated homogeneously with no detailed distinction between particular substances. In the group of patients declaring the use of opioids, there were both heroin and “compote” (a homemade extract of opioid alkaloids obtained from poppy straw decoction aka “Polish heroin”) users as well as tramadol users. Also, the people who declared taking various drugs belonging to the BDZ group were treated as one group.

There were also 3 specific cases of various chemicals use, among others, volatile solvents (1 case), Z-drugs (2 cases). These results are shown in Figure 1.



AMF – amphetamine; BDZ – benzodiazepines, NPS – new psychoactive substances.

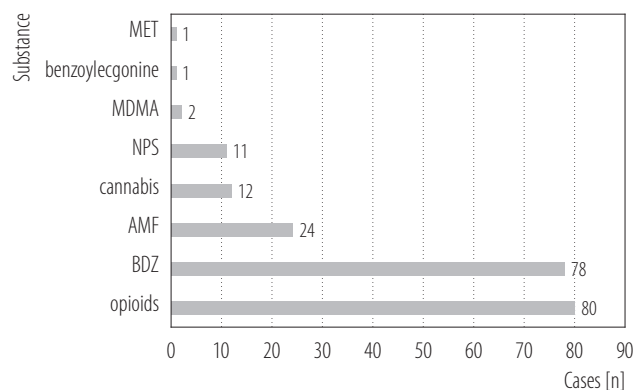
Figure 1. Last 48 h self-reported substance use in patients diagnosed with mental and behavioral disorders due to psychoactive substance use, Olsztyn, Poland

Symptoms were reported in 73 out of 116 patients during the physical examination. The range of symptoms represented by the patients was non-specific according to the type of intoxicating substances they had taken. Patients may have had one or several symptoms, or they could have no symptoms at all. Assessment of symptoms due to the above-mentioned conditions of this group (part of the group of elective admissions, individuals with substance use disorder – the possibility of developing tolerance) was not justified in this case. Symptoms in such cases may result from both the intake of any psychoactive substance and also be a consequence of addiction.

Results of blood and urine analysis

Only in 8 cases (7%) from the group of patients blood and urine tests did not show any of the psychoactive substances they were tested for. All patients with negative blood and urine tests belonged to the group of planned admissions.

In 12 (11%) out of 108 positive cases, only one substance was present. In the rest of the patients, >1 substance was



MDMA – 3,4-methylenedioxy-methamphetamine; MET – methamphetamine. Other abbreviations as in Figure 1.

Figure 2. Substances analytically confirmed in patients diagnosed with mental and behavioral disorders due to psychoactive substance use, Olsztyn, Poland

detected, while in single cases patients were positive for even 5 different groups of substances (NPS, AMF, BDZ, opioids, cannabis).

Apart from the substances representing the groups included in the questionnaire, the authors have also observed the presence of MDMA – 2 cases and methamphetamine (MET) – 1 case.

The results of blood and urine analysis of substances detected in this sample are presented in Figure 2.

New psychoactive substances were detected in 11 patients (including 3 different substances in 1 patient, 2 substances in 2 patients, and 1 substance in 8 patients). The following NPS were detected: MMB-CHMICA (2 cases), 3-chloromethcathinone (3-CMC) (2 cases), Ab-CHMINACA (2 cases), MDMB-CHMICA (3 cases), THJ-2201 (1 case), MMB FUBINACA (2 cases), PB-22 (4 cases). All detected NPS, except 3-CMC belonged to the synthetic cannabinoid group. In turn, 3-CMC, belonged to the group of synthetic cathinones.

In 5 cases, NPS was only found in the blood, in 3 cases only in the urine, while in 3 other cases it was found both in the blood and urine. Of these, in the latter group, other NPS were present in the urine and others in the blood.

The detailed information concerning NPS-positive cases is presented in Table 3.

In the group of 11 patients whose samples were positive for NPS, only 3 in anamnesis declared that they had taken these drugs. Two of them were admitted in emergency mode and 1 in elective mode.

A wide range of symptoms was found in the clinical examination of 10 patients from the NPS-positive group. These included: depressed mood, gait disturbances, tachycardia, agitation, weakness, insomnia, anxiety, fear, hallucination.

These symptoms were not typical for any specific group of psychoactive substances.

Due to discrepancies between anamnesis and analytical results, the authors decided to examine the data from toxicology tests of a group of patients declaring NPS intake during anamnesis. In a group of 13 patients who declared taking NPS, these substances were detected in the blood or urine of only 3 of them.

There has been a comparison made between NPS-negative and NPS-positive groups concerning the demographic data, as shown in Table 4.

The authors have not observed statistically significant differences in sex distribution between the study groups ($p = 0.564$, Fisher's exact test). The age analysis showed that the average age of patients who took NPS was 27.6 years (range 19–35 years). Such patients were usually 9 years younger than NPS-negative patients. This difference was statistically significant ($t = 3.22$, $p = 0.003$, Welch's t-test). The analysis of the age range showed that the percentage of NPS-positive patients was higher in younger age groups. There were no cases of NPS use in patients >40 years.

The authors have reported a slightly higher percentage of emergency admissions in the NPS-positive group compared to the NPS-negative. Due to the small number of patients in the examined group, this difference was not statistically significant ($p = 0.758$, Fisher's exact test).

Table 3. Characteristic of patients with analytically confirmed NPS use in a blood/urine sample and diagnosed with mental and behavioral disorders due to psychoactive substance use, Olsztyn, Poland

Psychiatric diagnosis	Self-reported substance use	Analysis results		Abnormalities on the medical examination	Participants (N = 11)		Admission type
		blood	urine		sex	age [years]	
F06.3, F13.3	BDZ	MMB-FUBINACA, BDZ	–	depressed mood, gait disturbances	male	34	elective
F19.3	none	THJ-2201	tramadol, BDZ	lack of symptoms	male	24	elective
F19.2	AMF, cannabis	PB-22, tramadol, AMF, BDZ,	tramadol, AMF, THC-COOH	tachycardia, agitation	male	29	emergency
F19.3	AMF, NPS	MMB-FUBINACA, AMF, BDZ	AMF, tramadol, 3-CMC, BDZ	agitation	male	25	emergency
F11.3	opioids	PB-22, tramadol, BDZ,	tramadol, BDZ	weakness, depressed mood	male	30	elective
F19.4	none	PB-22, AMF, BDZ	–	hallucinations	male	32	emergency
F19.3	none	PB-22, BDZ	MDMB-CHMICA, tramadol, BDZ	insomnia, anxiety, agitation	male	19	emergency
F19.3	AMF	AMF	3-CMC, AMF, tramadol	fear, anxiety	female	24	emergency
F19.3	NPS, AMF	AMF, BDZ	AB-CHMINACA, AMF, tramadol, BDZ	hallucination	male	35	emergency
F19.3	none	–	MMB-CHMICA, tramadol, morphine	fear, anxiety	male	20	emergency
F19.3	NPS	AMF, MDMB-CHMICA,	AB-CHMINACA, MMB-CHMICA, AMF	weakness, anxiety, depressed mood	female	32	elective

Abbreviations as in Figure 1.

DISCUSSION

This article aimed to assess the analytically confirmed presence of psychoactive substances, especially NPS in a specific group of inpatients with mental and behavioral disorders due to psychoactive substance use.

As expected by the authors, “old type,” “classic” drugs were dominating the study material. Only in 8 patients were none of the tested substances detected in the blood or urine. The current data concerning the popularity of individual drug groups differ from the data for the whole of Europe, where cannabis dominates, followed by cocaine and AMF [1].

In the current study group, opioids (69%) and BDZ (67%) dominated, followed by AMF (21%) and cannabis (10%). New psychoactive substances were detected in the blood

or urine in 11 patients (9% of cases). The significant contribution of opioids might be caused by the high addictive potential of this group. In the case of BDZ, it is due to high availability and popularity.

Interestingly, numerous studies have shown that opioid overdose over the years has been the main cause of death in cases of fatal poisoning in the population of drug individuals with substance use disorder in many countries [22].

The NPS were detected in 11 subjects, which constituted 9% of cases. The similar study, based only on anamnesis data, showed that 34% of the patients revealed contact with NPS in their lifespan [20]. The results of the toxicological analysis confirmed the presence of NPS in the blood or urine of 9% of tested patients. In our view,

Table 4. Demographic characteristics and type of admission of NPS-positive and NPS-negative patients diagnosed with mental and behavioral disorders due to psychoactive substance use, Olsztyn, Poland

Variable	Participants (N = 116)	
	NPS-negative	NPS-positive
Sex [n (%)]		
male	82 (78)	9 (82)
female	23 (22)	2 (18)
Age [years] (M)	34.9	27.6
≤20 years [n(%)]	5 (5)	2 (18)
21–30 years [n(%)]	49 (45)	5 (46)
31–40 years [n(%)]	32 (30)	4 (36)
>40 years [n(%)]	20 (19)	0 (0)
Admission to hospital type [n (%)]		
emergency admission	60 (57)	7 (64)
elective admission	45 (43)	4 (36)

such differences could be explained by the following reasons:

- In a given study the results included the use of NPS in general, regardless of the time (the examined patients could have taken NPS recently as well as in the distant past). Whereas, in the current study the authors analyzed only the blood and urine samples, which means that only the recent period was taken into account.
- A relatively narrow toxicological panel was utilized in the current study. Due to this, it cannot be excluded that some substances that had been taken could not be detected as they were not included in the screening.

Comparing the results of the current study with other studied populations, the results show a slightly higher number of NPS-positive results than in the groups of patients with recreational toxicity described by Vallersnes et al. [18], who detected NPS in 8% of cases. In contrast, Dines et al. [2] in a large multicentre study detected NPS in 5.6% of patients with overdose. In turn, a higher percentage of NPS-positive results in the event of an over-

dose of 14% of patients was obtained in the STRIDA project [15,16].

Among the substances detected in the study, SCRAs were prevailing. The SCRAs were especially popular at that time [1,10,12,17,18].

The analysis of the demographic data showed that the NPS-positive group was younger than the NPS-negative group. The difference was found to be statistically significant ($t = 3.22$, $p = 0.003$, Welch's t-test). This observation tallies with the data from other studies [7–16]. What is more, the frequency of emergency admissions of NPS-positive patients was slightly higher than those of NPS-negative. However, in this case, the difference was not statistically significant ($p = 0.758$, Fisher's exact test). The reason for the lack of statistical significance may be the small sample of NPS-positive people.

Large discrepancies were noted between the data obtained from the anamnesis and analytical tests regarding the type of psychoactive substances used. The reasons for this may be:

- subjects could take substances that were not included in the spectrum of the analysis, or
- as noted earlier, in Poland NPS constitute a large and diverse group of substances lumped together as “boosters.”

In addition, in the case of an illegal market, substances other than those declared by the seller are often bought. Therefore, it cannot be ruled out that some of those declaring taking NPS have actually taken substances classified as “classic” drugs, e.g., AMF. For example, often dried material of cannabis advertised as natural marijuana can be enriched with its synthetic derivatives, which could explain the case of a patient No. 3 who reported that she had taken cannabis and was diagnosed with PB-22 [23].

Other reasons include:

- subjects who have a problem with substance abuse may be uncertain of the time they last took NPS,
- the time of drug elimination from the bloodstream and urine in many NPS has not been established.

Regardless of attempts to explain the discrepancies found, such results indicate that anamnesis data on ingested substances should be treated with extreme caution.

The correlation between psychiatric diseases and consumption of “classic” psychoactive substances (alcohol, cannabis, opioids, and cocaine) are common and well documented [7]. Recent studies have noted a similar pattern for NPS abuse [9,10]. Consumption of traditional psychoactive substances (alcohol, cannabis, opioids, and cocaine) often co-occurs with other psychiatric disorders [10,24,25]. Potential NPS consumers are also found among psychiatric patients [26]. Literature, in turn, shows that the incidence of psychiatric diseases ranges from 30.5% [27] to 45% [28] in the population of people using drugs.

Meanwhile, in the current study, only one person had been diagnosed with psychiatric comorbidities (9%) in the NPS-positive group and in the whole group, there were 12 such cases (10%). The authors have not determined the reason for this discrepancy. It may be due to a different research methodology (in the case of the cited papers, the results were based on medical anamnesis data).

Limitations

There are some limitations to the study which need to be mentioned.

The first limitation is the relatively narrow toxicological panel. It includes 36 substances such as “old type classic” drugs and NPS. These substances have been selected as the most commonly used based on patient declarations and authors’ professional experience. For this reason, it cannot be excluded that some patients may have taken drugs which the authors did not screen for.

The next issue is related to the scope of information obtained from the respondents. One of the questions was: “Have you taken any psychoactive substances in the last 48 h?”

The pharmacokinetics of many illicit substances are known and well described, but for others such as NPS, this knowledge is poor. For this reason, the authors had to determine

the group of patients arbitrarily in terms of consumption time. It is, therefore, possible that some of the substances may not have been detected. At this point, it should be noted that the studied group of patients often do not have a very reliable approach to the sense of the passage of time. Hence, some simplification was made and the value of 48 h was arbitrarily assumed for the entire study group. It should be noted that in the case of classic drugs, the duration of their maintenance in urine or blood is established and may even be longer (especially BDZ, cannabis) than 48 h [29]. Therefore, in the case of substances other than NPS, the compatibility between anamnesis data and analytical results was not analyzed.

The last, but not least possible limitation of this study is the small size of the study group of patients, which consisted of only 116 people.

CONCLUSIONS

Classic drugs and medications like opioids and BDZ dominated in the examined material. New psychoactive substances were found in 9% of patients in this group. The NPS presence with the predominance of synthetic cannabinoids was similar in the group of patients addicted to psychoactive substances as, for example, in the population of recreational drug users or the population of patients with overdose.

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