https://doi.org/10.31925/farmacia.2022.3.7 **ORIGINAL ARTICLE**

TOXICOLOGY OF NEW PSYCHOACTIVE SUBSTANCES: AN INTERNATIONAL SURVEY ON THE EXPOSURE TO DRUG USE

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Abstract

Romania, among many countries, has been facing for the last 10 years a worrying increase of abuse substances use. Known as "legal highs" or "ethnobotanics", the new psychoactive substances (NPS), as they are scientifically known, are becoming more and more popular putting at risk a large part of the population. To collect more information regarding the exposure of the population to drug use (in particular NPS use and NPS' adverse effects), a survey was conducted in Romania and in EU and non-EU countries. 760 participants were surveyed in Romania and 80 participants from outside the country were included. High percentages in abuse substances use were obtained in both surveyed groups (group 1 – Romania, group 2 – outside Romania). Self-reported symptoms highlighted effects on various biological systems giving the specialists a possibility to identify a possible toxidrome in NPS consumption. Psychological effects are by far the most frequent after NPS intake. Yet, these self-reported symptoms may not be all related to NPS use as many users combine them with other similar substances or with alcohol and most of the users may not be aware of the drug they have taken. To better understand NPS epidemiology, community-based epidemiological surveys are needed.

Rezumat

România, printre alte multe țări, se confruntă în ultimii 10 ani cu o creștere îngrijorătoare a consumului de substanțe de abuz. Cunoscute sub numele de „legale" sau „etnobotanice", noile substanțe psihoactive (NSP), conform denumirii științifice, devin din ce în ce mai populare, punând în pericol o mare parte a populației. Pentru a colecta mai multe informații cu privire la expunerea populației la consumul de droguri (în special utilizarea și efectele adverse ale NSP), a fost realizat un sondaj în România, în țările UE și din afara UE. Au fost chestionați 760 de participanți în România și au fost incluși 80 de participanți din afara țării. Procente ridicate în utilizarea substanțelor de abuz au fost raportate în ambele grupuri chestionate (grupul 1 – România, grupul 2 – în afara României). Simptomele auto-raportate au evidențiat efectele asupra diferitelor sisteme, oferind specialiștilor posibilitatea de a identifica un posibil toxidrom în consumul de NSP. Efectele psihologice sunt de departe cele mai frecvente după administrarea NSP. Cu toate acestea, este posibil ca aceste simptome auto-raportate să nu fie în totalitate legate de utilizarea NSP, deoarece mulți utilizatori le combină cu alte substanțe similare sau cu alcool și este posibil ca majoritatea utilizatorilor să nu fie conștienți de drogurile pe care le-au autoadministrat. Pentru a înțelege mai bine epidemiologia NSP, sunt necesare anchete epidemiologice la nivel comunitar.

Keywords: NPS, survey, toxidrome, exposure

Introduction

Even though multiple surveys on drug use have been conducted in Romania and all over the world to obtain information regarding the prevalence and pattern of drug use amongst the population, this survey is one of the first to investigate the subjective adverse effects of new psychoactive substances (NPS) in Romania, whose primary objective is to highlight a possible toxidrome in NPS use.

Described as highly potent and harmful drugs by medical specialists, new psychoactive substances (NPS) are known by the population as "legal highs" [1] and have become easily available for the past few years, putting at risk a large part of the population. Some of these compounds target cannabinoid receptors and are called cannabimimetic or synthetic cannabinoids [2, 3, 4]. Synthetic cannabinoids can be purchased as "spice" or "K2" in the drug market or *via* the Internet [5, 6]. Cathinones, also known as "bath salts" or "plant food," are psychoactive drugs whose parent compound, cathinone, is a well-known stimulant that can be isolated from the Khat plant or produced by synthetic means [7, 8]. Cathinones have high

selectivity and strong activity for serotonin receptors and monoamine transporters [9, 10].

In Romania, NPS appeared on illicit marked in 2008 - 2009 and reached their peak in 2010 [11]. For the moment a downward trend was identified with stabilization in the last 3 years. This might be determined by legislative and control measures taken by the authorities but also by better information among the general population on the risks generated by drug use. According to the National Report on the Situation of Drugs in Romania 2020, a comparison has been done between General Population Survey (GPS) 2019 and previous studies (GPS 2013, 2016). Results have shown that there are increases for all three types of consumption (throughout life, in the last year and the last month). Compared with 2016, in 2019 the prevalence of use of any type of illicit drug has increased: throughout entire life – 7.6%/11.9%, in the last year – 4.1%/6.7%, in the last month - 1.8%/4.2%. The registered differences could be explained by either reviving interest in new psychoactive substances or the evolution of cannabis use, which continues the upward trend in Romania [12].

Similar, in Europe, according to ESPAD (European School Survey Project on Alcohol and Other Drugs) 2019, the prevalence of use of any type of illicit drug (cannabis, ecstasy, cocaine, crack, amphetamines, LSD or other hallucinogens, heroin, NSP) among 16-year-old students during lifetime is 11.8% (including non-prescription drugs – 12.4%). A percentage of 8.7% (8.1% – 2015) of 16-year-olds have experienced cannabis use throughout their lives while 3.2% experienced NSP, 2.8% solvents/inhalants, 1.8% cocaine, 1.7% LSD or other hallucinogens, 1.2% ecstasy, 0.7% heroin, 1.8% ketamine, 0.6% crack, 0.6% methamphetamine and 0.5% amphetamine [13, 14].

Due to the addictive character and mostly because many young people became ill or even died, in Romania was issued Law no. 194/2011 which forbade NPS possession and use [15]. However, the text of the Law is to be modified, and most likely the purchase and consumption of "legal highs" will be allowed, or at least less restricted in Romania which will increase the number of patients in hospitals. That is why NPS came back in the spotlight and more research in the field is needed.

To better understand the possible effects of NPS, the mechanism of action for synthetic cannabinoids and cathinones has been highlighted [16, 17]. Several studies have researched the mechanism of action for cathinones and synthetic cannabinoids [18, 19]. According to those, stimulants such as cathinones interact with monoamine transporters and mostly induce sympathomimetic adverse effects. Due to similarity with amphetamines and their interaction with several adrenergic and serotonergic receptors, the use of cathinones is being associated with mainly sympathomimetic toxicity manifested as agitation, tachycardia, hypertension [20, 21], and less frequently as lower levels of consciousness, hallucinations, hyponatremia, chest pain, palpitations, and nausea. Also, synthetic cathinones may cause skeletal muscle damage [9, 22].

Similar to Δ9-tetrahydrocannabinol (THC), the primary psychoactive constituent in cannabis, synthetic cannabinoids interact with CB_1 and CB_2 cannabinoid receptors and elicit cannabimimetic effects [23-25]. The endocannabinoid system is involved in various physiological functions, including cognition, behaviour, memory, motor control, pain sensation, appetite, cardiovascular parameters, gastrointestinal motility and immunoregulation. The receptor thought to drive the psychoactive effects of synthetic cannabinoids is the cannabinoid type 1 (CB_1) receptor. The psychoactive effects of synthetic cannabinoids are associated with a less desirable effect profile and more severe adverse effects compared with cannabis. The most common adverse effects of synthetic cannabinoids include agitation [26, 27], drowsiness, dizziness, confusion, hallucinations, hypertension, tachycardia, chest pain, nausea and vomiting [28-30].

Materials and Methods

To collect more information regarding the exposure of the population to drug use, in particular to NPS and their adverse effects, a survey was conducted in Romania and countries outside Romania. 760 participants were surveyed in Romania and 80 participants from outside the country were included.

The collection of information based on this questionnaire was done according to applicable General Data Protection Regulation (Regulation (EU) 2016/679 for Europe), USA Data Protection Laws and Regulations and Personal Information Protection and Electronic Documents Act (PIPEDA) for Canada.

The survey was conducted online using Google Forms in 3 languages: Romanian language („*Sondaj privind expunerea populației la consumul de droguri – România – 2021*" - the questionnaire targeted the Romanian population), English language ("Survey on the exposure of the population to drug use" - the questionnaire targeted the population of countries such as Australia, Asian countries, Belgium, Canada, Germany, Ireland, Italy, the Netherlands, Sweden, UK, US countries) and Spanish language *(„Encuesta sobre la exposición de la población al consumo de drogas"* - the questionnaire targeted the population of countries such as: Spain, Latin American countries, USA, Mexico, North America, South America, other). For further reference, we will refer to the results collected from the questionnaire in the Romanian language as of group 1 and for the results collected from countries outside Romania as of group 2.

Results have been collected during a period of $1^{1/2}$ months (mid - January - end of February) in Romania and during almost 2 months (end of January - mid - March) in countries outside Romania. Responses were limited to one answer *per* participant.

Survey design and objectives

The survey consisted of 45 questions, grouped into 2 categories. The first part of the questionnaire was addressed to the general population and consisted of questions that were meant to determine if the consumer belonged to a certain social group. Information such as country, gender, age, residency, education, income level, excess of energy, loneliness, relationship with friends, habits (attending bars/clubs/parties, drinking alcohol) was collected. Also, questions whose *primary objective* was to determine if the participant met the risk factors were included in the survey: curiosity in using drugs, knowing a person who bought/sold drugs, knowing a person who got hospitalized due to drug use, existence in the friends' circle of drugs users, antecedents in using drugs and reasons for repeating the experience. The first part of the survey also contained questions focused on assessing the "knowledge" of these new substances and their possible risks, assessing the opinion on their inoffensiveness and on legalizing them, identifying the exposure of the population to them, defining the prevalence of use but also outlining the recurrence and frequency along with main methods of use.

The second part of the questionnaire was addressed to drug users only, in this case to NPS users. The primary objective of the questions was to identify patterns of use (singular, associated with similar substances or with alcohol), to identify the effects desired by users when consuming these substances and to identify the adverse effects felt after consumption. The latter were classified based on the affected systems: cardiovascular, ENT (ear, nose and throat), gastro-intestinal, genitourinary, musculoskeletal, neurologic, ophthalmologic, psychological, sympathomimetic toxidrome and others.

When electing the adverse effects we considered the specific signs and symptoms reported in the literature by healthcare providers about patients with reported use of these products [7].

Participants

Participants who attended this survey were male and female, of ages over 14 years. The main inclusion criterion was access to internet platform to complete the survey. No more than one answer was accepted for each user. No email addresses were collected to meet the confidentiality requirements.

Substances of interest

Investigational substances were primarily NPS, cathinones and synthetic cannabinoids.

Statistical methods

All data analyses were performed using Microsoft Excel. Summary statistics were performed for overall subjective adverse effects (based on all affected systems) and statistical analyses were performed for each question included within the survey. Missing values (questions where the obtained result was zero) were replaced with "not applicable" (NA). Each category of results was expressed using the total number of responses received and percentage within the group for each of the two groups (group 1 and group 2). For each question, an overall number of responses was obtained that was also expressed in percentage (%).

Results and Discussion

The most results were collected from participants in Romania (760 participants), representing 90.47% of the total (840 globally). The majority were males, totalizing 658 participants (78.33%) in both groups: group 1 with 603 participants (79.3%) and group 2 with 55 participants (68.75%). The dominant age range was between 21 and 30 years (421 participants globally, 50.11%), followed by 204 (24.28%) participants with ages between 31 - 40 years, 121 (14.40%) participants with ages between 14 - 20 years, 77 (9.16%) participants with ages between 40 - 50 years, and only 17 (2.02%) participants had over 50 years old. The majority live in cities (735 participants globally, 87.5%) in both groups, 87.36% in group 1, and 88.75% in group 2. Regarding education and income, most of the participants have graduated from a university (721 participants globally, 85.83%), while 113 (13.45%) participants graduated from highschool (13.81% in group 1 and 10% in group 2), and only 6 (0.71%) participants (0.52% in group 1 and 2.5% in group 2) abandoned school after secondary school. 22.73% (totalizing 191 participants) declared to have financial issues (whether depend on their parents or can't cover daily expenses).

Researchers have identified several risk factors that, if present in the life of a teenager/young person, provide the right context and may increase the likelihood that he or she will be involved in drug use [14]. These were grouped into individual, family related and social risk factors. Our survey focused on some of the individual and social factors, as follows: excess of energy was felt by 156 participants (18.28% in group 1 and 21.25% in group 2), loneliness was felt by 165 participants (20.13% in group 1 and 15% in group 2), 316 declared they have many friends (35.78% in group 1 and 55% in group 2), 181 usually attend clubs and bars (20.52% in group 1 and 31.25% in group 2), 185 (22.02%) usually get bored without alcohol or drugs (21.71% in group 1 and 25% in group 2), 233 participants (27.73%) started using drugs as a curiosity (28.02% in group 1 and 25% in group 2), 75 (8.92%) of the participants increased alcohol intake/drug dose for a more intense effect (7.5% in group 1 and 22.5% in group 2), and 218 participants (25.95%) have experienced sudden

mood swings caused by alcohol/drug use (23.02% in group 1 and 53.75% in group 2). Regarding social risk factors, the outcomes of the survey were: 536 participants (63.80%) have a friend who has ever consumed drugs (63.68 % in group 1 and 65 % in group 2), and 400 participants (47.61%) know anyone who can procure drugs (47.76% in group 1 and 46.25% in group 2). Although 98.09% of the surveyed participants (totalizing 824 participants, 98.28% in group 1 and 96.25% in group 2) knew that drugs are dangerous and can lead to serious health problems and a majority of 80.83% (676 participants) do think NPS should not be legalized (80.39% in group 1 and 85% in group 2), 310 participants to survey (36.09%) have used drugs at least one time in a lifetime (35.92% in group 1 and 46.25% in group 2) and 27.73% (233 participants) started using drugs as a curiosity. More than that, 17.61% declared that obtaining drugs was easy (16.71% in group 1 and 26.25% in group 2). Almost half (44.64%) of the participants in this survey had an acquaintance with addiction issues (44.34% in group 1 and 47.5% in group 2) and 27.02% knew someone who got hospitalized or rehabilitated due to drug use (26.44% in group 1, 32.5% in group 2).

Regarding the use of drugs, most of the study participants (530) have never used drugs. 216 participants (25.71%) used drugs multiple times (24.86% in group 1 and 33.75% in group 2), while 100 participants (11.90%) used drugs only once. The majority didn't get hospitalized due to drug use (837 patients globally, 99.6% in group 1 and 100% in group 2). The reasons for repeating the experience among the participants who ever used drugs were: feeling good (162 participants globally, 18.68% in group 1 and 25% in group 2), 60 participants declared drugs are not additive (7.5% in group 1 and 3.75% in group 2), 43 participants declared drugs are not dangerous (4.73% in group 1 and 8.75% in group 2), and only 21 participants to survey declared they wanted to be cool (2.63% in group 1 and 1.25% in group 2).

Known as "legal highs" and sold as "bath salts" or "ethnobotanical drugs", the NPS are considered to be relaxing drugs rather than dangerous abuse substances. Yet, the majority of the study participants don't think these are inoffensive. Surprisingly, even though the majority of 81.19% have heard of ethnobotanical drugs, almost 44.52% (374 participants to survey, 43.42% in group 1 and 55% in group 2) don't have an opinion on their inoffensiveness/harmful effect.

Results of the survey outlined that most of the population has heard of drugs such as cannabis (777 reports – 92.5%, 94.07% in group 1 and 77.5% in group 2), cocaine (750 reports – 89.28%, 92.36% in group 1 and 60%), and heroine (717 reports – 85.35%, 88.81% in group 1 and 52.5% in group 2). NPS are yet unknown under the particular name of cathinones (58 reports – 6.90%, 6.31% in group 1 and 12.5% in group 2), but seem to be rather familiar under names such as ethnobotanical drugs (682 reports – 81.19%, 86.97% in group 1 and 26.25% in group 2), "Spice"/K2/Black Mamba (235 reports – 27.97%, 29.47% in group 1 and 13.75%), and "bath salts" (143 reports – 17.02%, 17.36% in group 1 and 12.5% in group 2).

Given the fact that in most of the cases the users don't know exactly what drug they have been taken, a prevalence of synthetic cannabinoids and cathinones use is difficult to measure. The outcomes of the survey regarding the prevalence of use are described in Table I.

Table I

Prevalence of use

Substance of abuse	Group 1 (%)	Group 2 (%)	Overall (%)
Bath salts*	0.92 (7/760)	2.5 (2/80)	1.07 (9/840)
Ecstasy	8.03 (61/760)	17.5 (14/80)	8.92 (75/840)
Mephedrone (M-CAT)*	1.44 (11/760)	3.75 (3/80)	1.66 (14/840)
Black Mamba*	0.13 (1/760)	NA	0.11 (1/840)
THC/Cannabis	41.31 (314/760)	20 (16/80)	39.28 (330/840)
Spice*	3.03 (23/760)	NA	2.73 (23/840)
MDPV*	0.26 (2/760)	NA	0.23 (2/840)
K2*	0.52 (4/760)	NA	0.47 (4/840)
HU-210*	NA	NA	NA
CP47,497*	0.13 (1/760)	NA	0.11 (1/840)
JWH-018*	0.13 (1/760)	NA	0.11 (1/840)
Flephedrone*	0.26 (2/760)	NA	0.23 (2/840)
AM series*	0.13 (1/760)	NA	0.11 (1/840)
Methedrone*	0.39 (3/760)	NA	0.35 (3/840)
Buthylone*	NA	NA	NA
None	65.61 (498/760)	76.25 (61/80)	66.54 (559/840)
Subtotal of NPS*	**7.36 (56/760)**	**6.25 (5/80)**	**7.26 (61/840)**

* synthetic cannabinoids or cathinone included within the survey

A percentage of 7.26% use of NPS under different market names ("bath salts", Mephedrone (M-CAT), Black Mamba, Spice, MDPV, K2, HU-210, CP47,497, JWH-018, Flephedrone, AM series, Methedrone, Buthylone) is to be highlighted, revealing that packaging of these products is often misleading or the interest in the users' chemical knowledge of what is using is not present. More than that most of these substances are labelled "not for human consumption", but there are mentions about similarity to other product's effects.

To determine the frequency of use, we also included within the survey a list of abuse substances giving the participant the possibility to tick for each substance the frequency of use during lifetime. We excluded the substances for which the only option "never" was ticked. The frequency in group 1 is represented in Figure 1. Similar results were obtained in group 2 – illustrated in Figure 2. By far, the most frequently used substances were cannabis and alcohol, but ethnobotanical drugs were also mentioned.

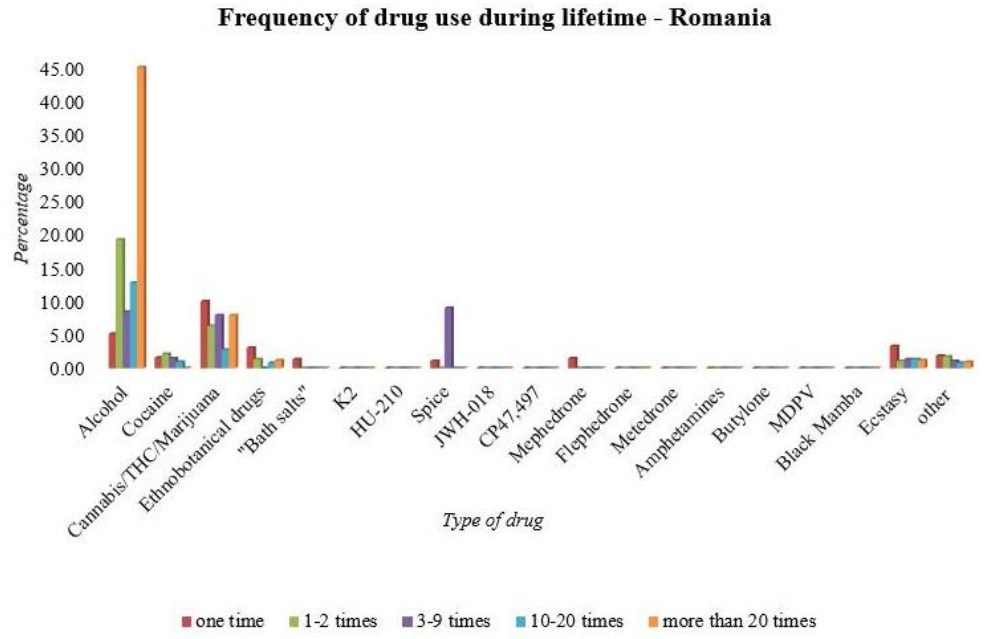

Figure 1.
Frequency of drug use during lifetime in Group 1

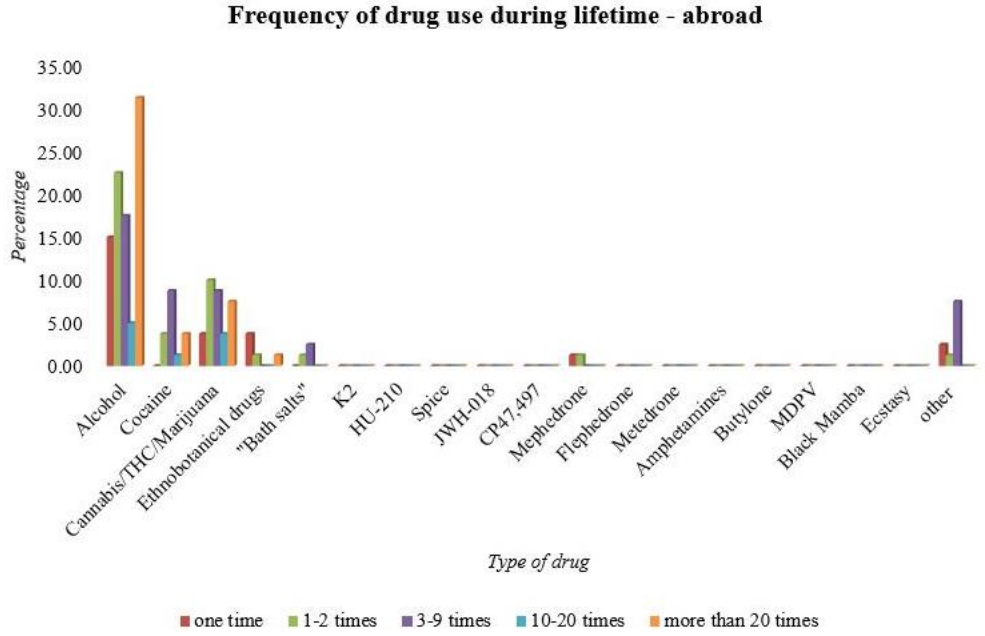

Figure 2.
Frequency of drug use during lifetime in Group 2

To take into consideration a possible addictive character, depending on the type of drug, a frequency of use more than 1 - 2 times is needed. Therefore, comparing the frequency of drug use during lifetime for the study groups, considering only the drugs with a minimum frequency of 3 uses during lifetime, and excluding alcohol, Cannabis registered higher values (probably due to its popularity among the illicit drug market), but ethnobotanical drugs also indicated high frequency *per* user.

Synthetic cathinones and synthetic cannabinoids are most commonly inhaled as the most responses regarding the route of administration were obtained for "smocking" – 295 results (78.24% of the participants who have ever consumed drugs used this route of administration, 35.26% in group 1 and 33.75% in group 2) and for "intranasal" – 51 results (13.52% of the participants who have ever consumed drugs used this route of administration, 5.26% in group 1 and 13.75% in group 2). 29 answers were received for sublingual use (3.42% in group 1 and 3.75% in group 2) while intravenous and intrarectal use was much more less mentioned (1 report for each route of administration, both in group 1). Intramuscular use was never reported among the study groups.

In most of the cases, users preferred to consume NPS only (229 participants globally – 78.15% of the participants who have ever consumed drugs, 80% in group 1 and 63.63% in group 2), but some of them (60 participants globally – 20.47% of the participants who have ever consumed drugs, 19.23% in group 1 and 30.3% in group 2) combined them with alcohol while others combined them with similar substances (14 participants globally – 4.77% of the participants who have ever consumed drugs, 4.61% in group 1 and 6.06% in group 2), increasing both desired effects and adverse effect's risk. Among participants to survey a total of 75 participants (8,92%) declared they used to increase alcohol intake with a drug dose to obtain a more intense effect.

NPS were used mostly for their relaxing effect (184 reports – 70.22%, 70.08% in group 1 and 71.42% in group 2) and the feeling of being "high" (158 reports – 60.30%, 60.68% in group 1 and 57.14% in group 2), as the generic name "legal highs" may suggest. Almost similar percentages were obtained for effects such as an increase in sexual appetite (62 reports – 23.66%, 24.78% in group 1 and 14.28% in group 2) and an increase in self-confidence (65 reports – 24.80%, 24.78% in group 1 and 25% in group 2). Also, NPS appear to be preferred by users for their effect in increasing energy (87 reports – 33.02%, 32.47% in group 1 and 39.28% in group 2) or even improving empathy (51 reports – 19.46%, 20.94% in group 1 and 21.42% in group 2). The relaxing effect and the sensation of "high" could be explained by the mechanism of action on CB_1 and CB_2 receptors, similar to cannabis. On the other hand, cathinones resemble amphetamine in their action, explaining the effect of increasing energy.

According to possible mechanism of action for the above mentioned NPS (synthetic cannabinoids and cathinones), there have been considered the adverse effects on various biological systems: cardiovascular, ENT (ear, nose, throat), gastrointestinal, genitourinary, musculoskeletal, musculoskeletal - extremity changes, neurologic, ophthalmologic, sympathomimetic toxidrome and other adverse effects, described in Table II, and on psychological system, described in Table III.

Table II

Distribution of adverse effects depending on the biological systems

Affected biological system	Group 1 (%)	Group 2 (%)	Overall (number of reports)
Cardiovascular	90.98 (111/122)	9.01 (11/122)	122
ENT	88.83 (159/179)	11.17 (20/179)	179
Gastrointestinal	87.85(94/107)	12.15(13/107)	107
Genitourinary	87.69 (57/65)	12.30 (8/65)	65
Musculoskeletal	82.46 (47/57)	17.54 (10/57)	57
Musculoskeletal – extremity changes	80.77 (42/52)	19.23 (10/52)	52
Neurologic	86.78 (105/121)	13.22 (16/121)	121
Ophthalmologic	90.52 (105/116)	9.48 (11/116)	116
Sympathomimetic toxidrome	90 (81/90)	10 (9/90)	90
Other effects	78.43 (40/51)	21.56 (11/51)	51

A number of 122 reports have been counted on the cardiovascular system (90.98% in group 1 and 9.01% in group 2, Table II). Among participants who had cardiovascular adverse effects, palpitations were the most common (106 reports – 86.88%, 88.28% in group 1 and 72.72% in group 2) but shortness of breath (45 reports – 36.88%, 36.03% in group 1 and 45.45% in group 2) and chest pain (17 reports – 13.93%, 13.51% in group 1 and 18.18% in group 2) were also mentioned.

On ENT (ear, nose, throat), from a total of 179 participants who reported ENT adverse effects (88.83% in group 1 and 11.17% in group 2, Table II), 161 felt dry mouth after consuming NPS (91.19% in group 1 and 80% in group 2), while 22 participants (12.29%) felt "nose burns" (10.69% in group 1 and 25% in group 2), 21 felt tinnitus (11.73% globally, 13.2% in group 1), 19 participants (10.61% globally, 9.43% in group 1 and 20% in group 2) felt nasal pain and 17 participants (9.49% globally, 9.43% in group 1 and

10% in group 2) oropharyngeal pain. A small percentage of 5.02% among participants (9 reports) who felt ENT adverse effects had epistaxis (3.77% in group 1 and 15% in group 2).

Regarding gastrointestinal adverse effects, a total of 107 participants to survey reported this type of reactions (87.85% in group 1 and 12.15% in group 2, Table II). The majority (74 reports – 69.15%, 69.14 % in group 1 and 69.23 % in group 2) had nausea, 53 participants (49.53% globally, 47.87% in group 1 and 61.53% in group 2) had vomiting, and almost equally, abdominal pain (25 reports – 23.36% globally, 21.27% in group 1 and 38.46% in group 2), and anorexia (27 reports – 25.23% globally, 28.72 % in group 1) were identified.

On the genitourinary system, 65 participants reported as having adverse effects (87.69% in group 1 and 12.30% in group 2, Table II). Most of them reported increased libido (52 reports – 80% globally, 85.96% in group 1 and 62.5% in group 2), but anorgasmia (13 reports – 20% globally, 14.03% in group 1 and 62.5% in group 2) and erectile dysfunction (6 reports – 9.23% globally, 8.77% in group 1 and 12.5% in group 2) were also reported.

On the musculoskeletal system, a total of 57 participants to survey reported adverse effects (82.46% in group 1 and 17.54% in group 2, Table II). 17 participants (29.82% globally, 34.04% in group 1 and 9.09% in group 2) had arthralgias, while 47 (82.45% globally, 78.72% in group 1 and 90.09% in group 2) had extremity changes. Among extremity changes, tingling was the most common effect (36 reports – 69.23% globally, 69.04% in group 1 and 70% in group 2) followed by numbness (20 reports – 38.46% globally, 40.47% in group 1 and 30% in group 2). Muscular tension and cramping were reported by 12 participants (23.07% of those who had adverse effects on the musculoskeletal system, 14.28% in group 1 and 60% in group 2) and only 4 participants reported discoloration (7.69% globally, 7.14% in group 1 and 10% in group 2).

Dizziness is the most common among *neurologic* adverse effects, counting 64 reports (52.89% globally, 55.23% in group 1 and 37.5% in group 2, Table II) from a total of 121 participants who had neurologic adverse effects (86.78% in group 1 and 13.22% in group 2). 59 participants (48.76% globally, 48.57% in group 1 and 50% in group 2) reported headache, 42 participants (34.71% globally, 33.33% in group 1 and 43.75% in group 2) had bruxism and 36 participants (29.75% globally, 30.47% in group 1 and 25% in group 2) had lightheadedness. An average percentage was obtained for memory loss (29 reports – 23.99% globally, 23.8% in group 1 and 25% in group 2) while only 18 participants (14.87% globally, 17.14% in group 1) to the survey felt tremor and 2 of them (1.65% globally, 1.9% in group 1) had seizures.

116 participants reported to have ophthalmologic adverse effects (90.52% in group 1 and 9.48% in group 2, Table II), mydriasis counting 93 reports (80.17% globally, 81.9% in group 1 and 63.63% in group 2) and 50 participants reported blurred vision (43.10% globally, 40.95% in group 1 and 63.63% in group 2). Nystagmus was also mentioned – 17 reports (14.65% globally, 14.85% in group 1 and 18.18% in group 2).

Among sympathomimetic toxidrom symptoms, 90 participants (90% in group 1 and 10% in group 2, Table II) had at least one of the followings: agitation (50 reports – 55.55% globally, 55.55% in group 1 and 55.55% in group 2), tachycardia (58 reports – 64.44% globally, 65.43 % in group 1 and 55.55 % in group 2), psychosis (26 reports – 28.88% globally, 30.86% in group 1 and 11.11% in group 2), hypertension (15 reports – 16.66% globally, 13.58% in group 1 and 44.44% in group 2) and seizures (2 reports – 2.22% globally, 2.46 % in group 1).

Among other type of adverse effects, 51 participants to survey (Table II) reported to have also symptoms as insomnia (35 reports – 68.62% globally, 72.5 % in group 1 and 54.54% in group 2), diaphoresis (15 reports – 29.41% globally, 25% in group 1 and 45.45% in group 2), nightmares (14 reports - 27.45% globally, 30% in group 1 and 18.18% in group 2). 4 participants to survey had characteristic body odor "mephedrone stink" (7.84% globally, 10% in group 1), 2 participants reported skin rash (3.92% globally, 2.5% in group 1 and 9.09% in group 2) while only 1 had fever (1.96% globally, 2.5% in group 1).

Regarding psychological adverse effects, these are by far the most common adverse effects reported within the survey. A complete description of these is included within the Table III below. The results are expressed as percentages for each adverse effect whithin every individual group. A total of 208 participants in the survey reported these types of adverse effects (186 reports in group 1, representing 89.42% and 22 reports in group 2, representing 10.57%). Most common symptoms were euphoria (114 reports – 54.80%) and sleepiness (77 reports – 37.01%). 73 participants (35.09%) felt an increase in energy and 71 (34.13%) felt empathetic. Agitation totalized 65 reports (31.25%). About a quarter of the participants reported having visual hallucinations (56 reports – 26.92%), fatigue (52 reports – 25%), and restlessness (53 reports – 25.85%). Panic was reported by 60 participants to the survey (representing 28.84% of the participants who reported psychological adverse effects). Lower percentages were obtained for symptoms such as anger – 19 reports (9.13%), auditory hallucinations – 25 reports (12.01%), depression – 28 (13.46%), dysphoria – 21 (10.09%) and formication – 28 (13.46%).

Overall, we classified the affected systems according the number of participants to survey who ever had

at least one symptom for each system. We concluded that psychological (208 reports, Table III), ENT (ear, nose, throat – 179 reports, Table II) cardiovascular (122 reports, Table II) and neurologic (121 reports, Table II) are the most common systems affected among participants to survey who used NSP.

Table III

Psychological adverse effects

	Group 1 (%)	Group 2 (%)	Overall (%)
Agitation	34.4 (64/186)	4.54 (1/22)	31.25 (65/208)
Anger	8.06 (15/186)	18.18 (4/22)	9.13 (19/208)
Anxiety	31.72 (59/186)	40.9 (9/22)	32.69 (68/208)
Auditory hallucinations	11.29 (21/186)	18.18 (4/22)	12.01 (25/208)
Visual hallucination	26.88 (50/186)	27.27 (6/22)	26.92 (56/208)
Depression	11.82 (22/186)	27.27 (6/22)	13.46 (28/208)
Dysphoria	10.75 (20/186)	4.54 (1/22)	10.09 (21/208)
Empathy	33.87 (63/186)	36.36 (8/22)	34.13 (71/208)
Euphoria	53.22 (99/186)	68.18 (15/22)	54.80 (114/208)
Fatigue	23.65 (44/186)	36.36 (8/22)	25 (52/208)
Formication	15.05 (28/186)	NA	13.46 (28/208)
Increased energy	35.48 (66/186)	31.81 (7/22)	35.09 (73/208)
Increased concentration	24.73 (46/186)	27.27 (6/22)	25 (52/208)
Decreased concentration	29.56 (55/186)	22.72 (5/22)	28.84 (60/208)
Sleepiness	41.39 (77/186)	NA	37.01 (77/208)
Panic	30.64 (57/186)	13.63 (3/22)	28.84 (60/208)
Paranoia	22.58 (42/186)	13.63 (3/22)	21.63 (45/208)
Restlessness	25.8 (48/186)	22.72 (5/22)	25.48 (53/208)

Considering all reports and the frequency of a particular symptom had been reported, a total of 2404 reports have been counted. The number of reports is bigger than the sum of participants *per* affected symptom because one participant could have had more symptoms for each system.

As expected, the most common adverse effects were: dry mouth, euphoria, palpitations, mydriasis, sleepiness, nausea. High frequency was also determined within symptoms such as increased energy, empathy, agitation, anxiety, dizziness, headache, visual hallucinations, panic, tachycardia.

Study limitations

Extrapolating the findings from this survey to NPS use in the general population of abused drugs users may be constrained by few limitations. Firstly this study was conducted in unequal groups of participants. Although surveys are being run all over the world, further surveys with the same pattern of questions should be run globally. Secondly, people are in general cautious when it comes to declaring illegal use of substances. Thirdly, most "legal highs" are sold in small packages, without a label. Therefore participants to survey who used drugs have declared a specific substance use based on the information the dealer had provided them verbally. This is why a certitude regarding the precise composition of the sample can not be ensured. Finally, all adverse effects, although based on previous studies from literature, have been subjectively selected by participants to survey. Not having knowledge in medical specialties, it's likely that some of the adverse effects identified by participants to the survey to not have been 100% accurate. Therefore, further studies are required to investigate the use of these products in an ambulatory setting.

Conclusions

This survey demonstrates that NPS although very popular on the illicit drug market are yet unknown in terms of composition. It also demonstrates that in terms of the level of exposure, all social classes are being affected. This is the first survey run in Romania to investigate both exposure of the population to drug use and adverse effects of NPS. Regarding adverse effects of new psychoactive substances, the results from the survey are consistent with findings from scientific literature in the field.

Conflict of interest

The authors declare no conflict of interest.

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