Knowledge and use of Novel Psychoactive Substances in Italy: a survey-based study in the general population

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- **Author contribution:** Caroline Zangani conceptualized the research. Protocol and material preparation was performed by Armando D'Agostino, Barbara Giordano, Caroline Zangani, and Edoardo Giuseppe Ostinelli. All the authors contributed to the diffusion of the survey. Caroline Zangani and Edoardo Giuseppe Ostinelli performed statistical analyses and drafted the manuscript. All the authors contributed to finalise the paper and agreed to the final version.

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Abstract

BACKGROUNDS: In this study, we aimed to identify the current trend of NPS consumption in Italy, the level of knowledge about NPS in the general population, and to explore the presence of risk factors for a lifetime NPS misuse.

METHODS: We conducted an anonymous online survey, administered to a large sample of people of any age living in Italy, asking for their knowledge about NPS as well as their history of drug use. Descriptive statistics were reported, and regression analyses were performed to identify risk factors for lifetime use of NPS.

RESULTS: A total of 1097 individuals gave a valid response to the survey. A lifetime use of NPS was reported by 13.5%. Multivariate regression analysis showed that male gender (OR 2.33, 95%CI 1.52-3.55), homosexual sexual orientation (OR 2.52, 95%CI 1.21-5.27), a use of emergency services due to alcohol (OR 3.38, 95%CI 2.23-5.12), and previous contact with mental health services (OR 1.58, 95%CI 1.04-2.41) were risk factors for a lifetime use of NPS ($p< 0.05$).

CONCLUSION: An improvement of preventive strategies and simplified access to information on NPS, especially tailored to individuals at increased risk of misuse, could slow diffusion of NPS and avert the consequences of substance use.

Keywords: novel psychoactive substances; survey; substance abuse; NPS; legal highs.

1. Introduction

Sustained by a rapidly increasing technological development and the rise of e-commerce, the scenario of psychoactive substance use has unexpectedly changed. Starting from the 1990s, a growing amount of novel psychoactive substances (NPS) have been produced and sold in the last decades (UNODC, 2014). Given this rapid turnover, NPS commonly evade law regulations, secondarily affecting

policymaking and ultimately clinicians, who are often inadequately informed on the consequences of their use (Simonato et al., 2013).

By definition, NPS are substances not controlled by the 1961 and 1971 conventions act on narcotic and psychotropic substances, but that may pose a public health threat (UNODC, 2013).

Major chemical groups of NPS are synthetic cannabinoids (or cannabimimetics), synthetic opioids, phenethylamines, synthetic cathinones, stimulants, tryptamine derivatives, GABA-receptors agonists, phencyclidine (PCP) derivatives, piperazines, herbal products, and medicinal products (Schifano, 2015; Schifano et al., 2021a). These drugs are synthesized by continuously modifying a pool of basic chemical structures and creating new molecules that wax and wane from the drug market in an endless turnover (Guirguis, 2017). The majority of the substances reported to the UNODC Early Warning Advisory (EWA) until December 2019, were stimulants, followed by synthetic cannabinoid receptor agonists and classic hallucinogens with a notable increase in synthetic opioids in recent years (UNODC, 2020).

To date, only a minority of NPS has been analysed in preclinical studies, and their effects are often unpredictable (Abdulrahim & Bowden-Jones, 2015; Orsolini et al, 2019). The desired effects more frequently reported by users can be divided in three categories: stimulant effects (e.g., euphoria, increased energy and alertness, fatigue reduction), hallucinogen effects (e.g., vivid auditory and visual hallucinations, change in time and space perception), and empathogenic effects (e.g., feeling expansion, sense of unity with the world) (Assi et al. 2016).

Around 120 countries and territories from all regions of the world have reported one or more NPS up to now (UNODC, 2020). By December 2019, the UNODC EWA has received more than 950 reports on NPS from Governments, laboratories, and partner organizations (UNODC, 2020). Available data suggest that the use of NPS in Italy has recently faced a sharp increase. In 2011, the recorded lifetime prevalence of NPS use in youth was 0.8% (Eurobarometer, 2011), growing steadily until an estimated rate of 4.7% in 2015 (Martinotti et al., 2015). In the same year, the previous-year consumption of NPS among Italian students was around 5% (ESPAD, 2015). Moreover, findings in youth suggested an

association between NPS use and binge-drinking behaviours (Eurobarometer, 2011).

Information on the consumption and diffusion of NPS are commonly retrieved from surveys (ESPAD, 2015; Martinotti et al., 2015; Vento et al., 2014), or through seizures and controls of the law enforcement (UNODC, 2014). Sometimes a new substance is identified after the report of an incident of mass-poisoning or a series of deaths in a specific location (Logan et al. 2017). Routine drug screenings are usually not able to find new substances, resulting in a high percentage of false negative tests (Logan et al. 2017).

Despite research on NPS is constantly growing, evidence on the diffusion of NPS is still limited and mostly focused on youth. No recent data on the level of awareness and abuse of NPS in the Italian general population is currently available. In light of the above, we hypothesised that NPS consume in Italy would follow a similar pattern, with a sharp growth since the last available data (i.e., 2015) and a low level of awareness in the general population. Moreover, previous studies argued that motivation to use NPS may be different within user groups (Benschop et al., 2020), ranging from curiosity to novelty-seeking and coping strategies (Orsolini et al., 2017; Soussan et al., 2018). This may be related to specific characteristics of NPS users which may vary over time and across nations. However, reliable data on putative risk factors for NPS-related use are lacking.

We developed an anonymous online questionnaire, administered to a large sample of people of any age living in Italy. In this study, we aimed to identify the current trend of NPS consumption in Italy, the level of knowledge about NPS in the general population, and to explore the presence of risk factors for a lifetime NPS misuse.

2. Methods

2.1 Participants

The questionnaire was addressed to the general population. We only included participants currently living in Italy. No further restriction was applied.

2.2 Questionnaire

A free website for creating professional surveys (SondaggioOnline, 2019) was used to develop the questionnaire.

The questionnaire was anonymous and written in plain language Italian. It included 37 principal questions and 11 optional sub-questions, divided into four domains. The first two domains collected data on demographic characteristics and life habits. In the third section, there were questions about the mental health history, while the last section explored the knowledge of drugs and drug market, and the drug use history of the responders.

To prevent users from completing the questionnaire twice, the website automatically blocked the IP addresses of the survey's participants. No IP address information was stored or collected by the authors.

In the list of available substances, we included the fake drug "Relevin" to check the truthfulness of collected data and test reliability of responders (Andrade 2012; EMCDDA, 2002). Participants declaring the use of Relevin were therefore excluded from our analyses.

The full questionnaire is available as supplementary material freely accessible at https://github.com/carolzangani/SurveyNPS.git.

2.3 Procedure

All the study procedures described were approved by the University of Milan Ethics Committee before its starting date.

The data were collected between the 4th of April and the 4th of October 2019.

Participants were recruited by word of mouth, or by visiting a dedicated website. Announcements with the web link to the survey were posted on the main social media (i.e., Facebook®; Twitter®; Instagram®), chat apps (e.g., Whatsapp®; Telegram®), and by flyers distributed in different public spaces (e.g., hospital, university, shops, station).

Before accepting to take part in the survey, individuals were presented with a participant information sheet containing details on the study purpose, relevant contact details, privacy policy, and management of collected data. Upon agreeing to take part into this study, individuals were able to answer our

questionnaire. The questionnaire could be interrupted at any time, without resulting in the exclusion from the study.

2.4 Data collection

At the closure of the survey, de-identified data were collected in a secure storage accessible only to the authors. Each questionnaire was checked to verify the truthfulness and likelihood of the answers. Questionnaires with improbable (e.g., participants declaring use of Relevin) or clearly fake answers were therefore excluded from our analyses.

2.5 Statistical analyses

We collected and summarized the demographic characteristics (e.g., age, gender, education levels) as both raw numbers and proportion of the total sample.

We performed a series of simple bivariate and multivariate logistic regressions to identify possible associations between the characteristics of the sample population (independent variables) and the use of NPS (dependent variable). The same procedure was used using conventional drugs as the dependent variable. We employed the following variables of clinical relevance in the bivariate models:

- Current use: age, gender, sexual orientation, nationality, parents' nationality, housemate, living conditions, education level, work, monthly income, lifetime access to emergency departments (EDs) due to alcohol, lifetime access to EDs due to illicit drugs, psychiatric history, psychiatric history in the relatives, binge episodes of alcohol consumption in the previous 6 months, cigarette smoking in the previous 6 months.
- Lifetime use: gender, sexual orientation, nationality, parents' nationality, education level, lifetime access to EDs due to alcohol, lifetime access to EDs due to illicit drugs, psychiatric history, psychiatric history in relatives.

We then included variables showing a statistically significant association in the subsequent multivariate logistic regression analysis. Finally, we produced a second multivariate model which only included variables with a statistically significant association in the previous multivariate analysis. To evaluate the adequacy of the models, we employed the following measures: the Hosmer-Lemeshow test to

evaluate whether the models are well calibrated, the McKelvey and Zavoina's pseudo R2 as a measure of interpretation of explained variance (Long, 2014), and the Bayesian Information Criterion (BIC) to compare the multivariate models in terms of explanatory power (Ostuzzi et al., 2018). Finally, we retained the statistically significant multivariate model with a non-statistical Hosmer-Lemeshow Chi2 test and the lower BIC values.

In order to address the statistical complete and partial separation issues, we performed a sensitivity analysis with a Firth's penalised logistic regression for rare events. We followed the same procedure outlined above, starting with bivariate models on the same set of variables to evaluate two multivariate logistic regression models.

We estimated the measures of effect from predicted probabilities from the logistic model (relevant to the use of NPS) to infer the risk-based associations. We performed a marginal standardization method to calculate the predicted probabilities as a weighted average separately for different levels of exposure, prevalence ratio and difference estimates. We preferred this technique over the prediction at the modes and prediction at the means not to limit our inference only to the relevant stratum of observations (Lane & Nelder, 1982).

The statistical analyses were performed with STATA 14.0 (Statacorp, 2015) and R (R Core Team, 2017).

3. Results

Overall, 1101 individuals responded to the survey, only four of which were excluded due to invalid answers (i.e., reported use of Relevin), while 918 of the remaining 1097 participants completed the questionnaire (83.68%).

3.1 Demographic characteristics

The relevant characteristics of the sample are summarized in Table 1. The mean age of the sample was of 31.31 (± 9.81), with an age range between 16 and 72 years. The majority of the sample was composed by females (57.3%), while heterosexuality was the most reported sexual orientation (89.48%).

The sample was almost completely composed of Italians (97.84%) and 95.31% reported having both Italian parents.

A large part of the sample had received a higher secondary (33.81%) or higher-level education (bachelor degree 13.54%, master degree 33.62%, post-graduate degree 13.83%). The majority of participants had a work as either an employee (48.13%) or an independent/freelance worker (15.08%). About 299 participants (28.72%) were students. The monthly income ranged between 1201€ and 2300€ for over a third of the study population (35.64%).

In terms of living conditions, almost half of the participants lived with their family of origin (46.63%) and 23.51% with a partner. Over two thirds of responders lived in an own-property house (66.48%).

3.2 Life habits

Just under a third (30.7%) of the sample smoked tobacco, mostly cigarettes/hand-made cigarettes (219 and 119 participants, respectively). Coffee was consumed by 87.22% of participants, whereas 63.53% drank tea, and only a minority (6.47%) consumed energy drinks regularly.

Overall, 83.92% of responders reported alcohol consumption in the six months preceding the survey, with a mean weekly intake of 3.05 (±3.35) glasses of wine, 2.73 (±3.143) beers, and 1.73 (±1.75) cocktails. Almost a third of the responders (30.14%) reported at least one episode of binge drinking in the previous six months, and a lifetime history of memory loss, loss consciousness or help from a health professional (i.e., first aid, emergency department) due to alcohol abuse (31.32%).

3.3 Mental health history

Over one third of responders (35.20%) had a previous contact with a psychologist, 7.22% had a previous contact with a child or adult psychiatrist, and 3.46% with a speech therapist. Overall, 52.69% of the sample did not report a previous contact with a mental health professional.

< Insert Table 1 here>

3.4 Drug knowledge

As summarized in Figure 1, all traditional drugs of abuse were known the majority of the sample, with cocaine on top (95.76%). Among NPS, popper (63.57%), oxycodone (55.83%), and ketamine (62.13%) were known by more than half of the responders, while knowledge of Salvia divinorum, mephedrone, GHB, and PCP was reported by a minority (24.87%, 21.98%, 21.16%, and 18.78%, respectively). As for the others, only BZP, NBOMe, khat, and ocfentanyl were known by more than 10% of the participants.

Information about drugs (Appendix 1, Table S1) was retrieved by participants mostly through television and social media (television programs 69.31%, social network 44.49%, Internet 38.52%) or talking with friends (64.36%). Only few responders searched information on psychonauts' websites (8.03%) or in specialized shops (2.68%).

The majority of the sample was aware of the possibility of buying drugs in street markets/parks (79.90%) or clubs (72.17%). About a third of the sample (32.29%) was aware of the possibility to buy drugs on the Internet. Finally, the 78.47% knew at least one person that had used at least one substance in their lifetime (Appendix 1, Table S2). In this case, the most consumed substance was THC (69.37%), followed by cocaine (60.19%). Among NPS, the most consumed drug was popper (26.10%).

<Insert Figure 1 here>

3.5 Drug use

Almost half (48.11%) of responders had consumed any substance of abuse at least once, while 13.5% reported a lifetime consumption of an NPS.

Among traditional drugs of abuse consumed by study participants, the most reported was THC (46.07%), followed by cocaine (9.35%), popper (9.10%) and MDMA (7.84%). The lifetime use of the other substances was ≤ 5%, with LSD (5.08%), amphetamine (4.35%), ketamine (3.58%), and Salvia divinorum (3.48%) on top. For the remaining substances, consumption was reported by ≤ 1% of the

sample. None of the responders reported having ever used alpha-PVP, methoxetamine, ocfentanyl, nor PCP (Figure 2).

<Insert Figure 2 here>

The co-occurrence pattern of misuse is visualised in Figure 3. As shown, the use of an NPS is frequently associated with the use of either another NPS or a traditional drug.

Among all study participants, 5.23% reported having taken an unknown drug (i.e., to consume a drug without knowing the nature of it) at least once, whereas only 1.53% reported the need of medical assistance (i.e., emergency medical service) following the use of any substance of abuse (excluding alcohol).

<Insert Figure 3 here>

3.6 Regression analysis

We compared the current use of NPS for a number of clinically relevant and available variables (Table 2). Five independent variables were significantly associated with a current use of NPS at the bivariate analyses. The multivariate logistic regression model confirmed a statistically significant association for the Italian nationality variable only (OR 0.07, 95%CI 0.13 - 0.37). This model showed a M&Z pseudo-R2 of 0.17 with a BIC value of 200.431. We confirmed the robustness of our findings running a Firth's penalised logistic regression, with the exception of living with the family of origin resulting statistically significant in the sensitivity model with the lower BIC value (Appendix 1, Table S3).

<Insert Table 2 here>

Table 3 shows the results for the bivariate analyses on the lifetime use of NPS, with eight variables

showing a statistically significant association. The following multivariate model resulted in a statistically significant association with the following variables: male gender (OR 2.33, 95%CI 1.52-3.55), homosexual sexual orientation (OR 2.52, 95%CI 1.21-5.27), lifetime access to ED due to alcohol (OR 3.38, 95%CI 2.23-5.12), and lifetime use of mental health services (OR 1.58, 95%CI 1.04-2.41). Our model showed a M&Z pseudo-R2 of 0.17 with a BIC value of 650.481 The sensitivity analysis with the Firth's penalised logistic regression model confirmed these variables as statistically significant (Appendix 1, Table S4).

<Insert Table3 here>

Analysing the use of traditional drugs, we found that 11 independent variables were significantly associated with a current use of traditional drugs at the bivariate analyses. Of them, a statistically significant association was confirmed in the multivariate logistic for male gender (OR 2.33, 95%CI 1.41 – 3.88), lifetime access to ED due to alcohol (OR 2.41, 95%CI 1.45 – 4.00), and nicotine consumption in the previous six months (OR 4.36, 95%CI 2.65 – 7.19). This model showed a M&Z pseudo-R2 of 0.30 with a BIC value of 461321 (Appendix 1, Table S5).

The bivariate analyses on the lifetime use of traditional drugs found seven statistically significant association. In the multivariate model, the variables resulted in a statistically significant association were male gender (OR 1.73, 95%CI 1.25-2.40), lifetime access to ED due to alcohol (OR 2.93, 95%CI 2.09 – 4.12), and lifetime use of mental health services (OR 1.79, 95%CI 1.33 - 2.22). Our model showed a M&Z pseudo-R2 of 0.14 with a BIC value of 970.409 (Appendix 1, Table S6).

Based on our logistic model, participants who accessed EDs due to an alcohol-related issue had a 6.5% of using a traditional drug (compared to 4.0% for those who never did), and a 23.5% predicted probability of using an NPS (compared to 8.7% for those who never did). Overall, the prevalence ratio between the two categories was 1.63 (95%CI 1.39 – 1.87) for traditional drug use and 2.7

(95%CI 1.78-3.62) for NPS use, with a prevalence difference of 25.1% (95%CI 17.5 – 32.7) and 14.8% (95%CI 9.4-20.1), respectively (Table 4).

4. Discussion

The present study investigated knowledge and use of NPS in Italy, showing the former to be highly variable, depending on the specific substance, and the latter to be in approximately 1 every 7 participants.

4.1 Demographic characteristics

NPS-related habits were investigated across all age-classes, with 93.44% responders between 15 and 64 years of age and over two thirds between 16 and 34 years old. Because the questionnaire was delivered through the internet, the recruited population might be skewed towards more tech-savvy users, resulting in a mean age slightly above 30 years old. To note, youngsters and adults proficient with the use of internet are thought to be the target users of NPS, with our sample characteristics being consistent with those previously reported in the available literature (Palamar, 2016; Soussan & Kjellgren, 2016).

4.2 Drug knowledge

Although television and social media were the most reported means of access to information on drugs, the majority of our sample was unaware of the existence of specialised blogs and dedicated markets, and of the possibility of buying substances online. This evidence shows how the information on NPS accessible to the general population is still poor. Since the prevalence of NPS sold in both the surface- and deep-web is likely to increase (EMCDDA, 2017), the development of a publicly wide awareness on NPS should be prioritised in the national preventive and harm-reduction strategies.

Interestingly, the top-tier substances in terms of knowledge were those that have been used for decades but are still nowadays considered “legal highs” (e.g., popper, ketamine, GHB). Except for mephedrone, knowledge on synthetic cannabinoids and cathinones, the most used NPS categories in Europe (EMCDDA, 2019), was rare.

4.3 Drug use

The above findings are consistent with self-reported individual consumption. The observed 13.5% lifetime use of NPS in our sample is in line with a previous report involving 168 respondents, in which 14% were NPS users (Deligianni et al., 2017). In our survey, the most used NPS were popper, ketamine, and Salvia *divinorum*, while the majority of the remaining NPS had a consumption prevalence ≤ 1%. These results are in line with a recent survey reporting a lifetime use of synthetic cannabinoids between 0.2% and 4% in the general population (Zhao et al., 2017). Moreover, a previous Italian survey (Martinotti et al., 2015) found the prevalence of NPS use to range between 0.1 and 1.2%. In contrast with our findings, the prevalence of mephedrone use in this sample was of 3.3%. However, the authors suggested that a wide diffusion of mephedrone in the sample was due to the presence of an illegal mephedrone refinery in the analysed geographic area. The use of popper has been mainly reported in specific subpopulation such as men with homosexual or bisexual orientation (Vaccher et al., 2020; Zhao et al., 2017). In this population, up to two third of the subjects reported a lifetime use popper (Vaccher et al., 2020).

Taken together with the available literature, our results might imply a lag in the Italian drug market changes, compared to other European nations. Therefore, NPS that are currently widely used in other countries might broaden their market in Italy in upcoming years. For example, mephedrone has been one of the most popular drugs in the UK since the early 2000s, and was banned in 2010 (Schifano et al., 2011), but the prevalence in our sample was of 0.76%. Healthcare workers and policymakers should therefore focus on available international longitudinal data to develop and implement effective strategies to prevent the diffusion of NPS, broadening the awareness of the general population on this topic. To do so, the identification of high-risk user groups is instrumental to develop tailored harm-reduction strategies.

4.4 Regression analyses

Meta-regression analyses highlighted some at-risk categories among consumers, such as males, homosexual individuals, people with alcohol-related risky behaviours, and people who had a previous

contact with mental health professionals. Although data on an association between use of traditional drugs and male gender are robust (Midgley et al., 2018; Schilling et al., 2017), available evidence on NPS is scarce and of lower quality. A previous US survey reported that males were at higher risk for NPS use (Palamar et al., 2015), coherently with our findings.

The use of NPS has been previously associated with a previous mental health history and the prevalence seems higher in individuals with an active psychiatric disorder (Neicun et al., 2020; Schifano et al., 2015). Moreover, the use on NPS has been anecdotally associated with several psychopathological consequences (Schifano et al., 2021b) and suicide (Chiappini et al., 2021). In our sample, most individuals with a previous contact with a mental health professional reported a contact with a psychologist. Interestingly, this may imply that a high risk of misuse of NPS is not limited to people with a serious mental illness, but it may also affect individuals with a psychological distress. Indeed, consumers self-reported use of novel substances as a strategy to cope with sleep problem, depression, anxiety, and stress related problems (Soussan et al., 2018).

Dangerous use of alcohol has previously been associated with both traditional drugs and NPS use (Martinotti et al., 2015; Patrick et al. 2016). Drug use was predicted by alcohol use in several high-risk population, such as young adult (Mbaga et al., 2018), homeless individuals (Santa Maria et al., 2017), and ethnic minorities (Griffin et al., 2019). In line with previous data, our study showed that having requested assistance of an emergency service due to alcohol abuse might be an important risk factor for the use of NPS. Based on our model, it might contribute up to an almost three-fold risk of lifetime use of NPS.

Interestingly, comparing categories at-risk for either traditional drugs or NPS use, they were comparable except for having a homosexual sexual orientation. This category has been found significantly associated to the use of NPS but not with traditional substances. A previous study found that gay and bisexual men reported a higher use of mephedrone compared to the other sexual orientations (Kelly et al., 2013). Although a recent review showed that sexual minority youth are at greater risk for substance use and misuse compared to their heterosexual peers (Mereish, 2019), no

evidence exists so far for the specific use of NPS. Available evidence is usually not stratified by sexual orientation, or conversely drugs habits are limited to sexual minorities subgroups only, without data on individuals with other sexual orientations (Lea et al., 2012; Vaccher et al., 2020). Our findings show that individuals who identified themselves as being homosexual may be at higher risk of NPS use compared to other sexual orientations. The use of substances in this group has been associated with recreational purposes (Wood et al., 2012), such as "chemsex" parties (Bourne et al., 2018; Vaccher et al., 2020). Chemsex is defined as the use of substances before or during sex encounters to facilitate, prolong, and/or intensify the sexual experience (Bourne et al., 2015). Indeed, the use of the most reported NPS in our sample (i.e., popper and ketamine) have been associated with chemsex (Maxwell et al., 2018) and substance-linked sex (Lawn et al., 2019). This finding highlights that chemsex could be widespread in Italy albeit scarcely reported (Anzilotti et al., 2020).

4.5 Limitations

Some limitations should be considered when interpreting our findings. First, the snowball sampling technique may have introduced a selection bias, recruiting a high percentage of medical students and young doctors, and mostly Italians. To limit this, we improved the dissemination using open-access social media and distribution of flyers to the general population. Moreover, although educational levels (Perez et al. 2018; Schepis et al. 2018) and ethnicity (Debnam et al., 2018; Penney et al., 2016) have been directly and indirectly associated with drug use, their role in NPS use prevalence is uncertain (Debnam et al., 2018; Orsolini et al., 2015; Rajan et al., 2018).

Second, we are aware that the relatively low event rate of NPS use could have introduced separation and quasi-separation issues in our statistical analyses. To account this, we performed Firth's penalised logistic regression bivariate and multivariate models, allowing use to compare and test the robustness of our findings. Nonetheless, the findings on current use failed to show significant results, as Italian nationality does not seem a reliable factor given the extreme paucity of the data and the absence of its confirmation in the lifetime use analysis.

Finally, access to emergency services due to alcohol was considered a risk factor for NPS use in our

analyses. This implies an assumption of directionality, based on the higher diffusion of alcohol (Roderick et al., 2018), so alcohol-related risky behaviour might be considered to increase the risk of NPS use. However, the use of alcohol and NPS has been extensively reported in cross-sectional studies (Martinotti et al., 2015; Patrick et al., 2016) and might be more conservatively considered a co–occurrence.

4.6 Conclusions

Policy makers should address at-risk individuals to raise their awareness about NPS. A qualitative study analysing discussions on internet forums found that NPS users were particularly interested in how to reduce the harms associated with drug consumption (Soussan & Kjellgren, 2014). Strategies oriented to share information on safer consumption and NPS-associated harm are crucial. Internet forums may be targeted from secondary prevention strategies, disseminating evidence-based information (Soussan & Kjellgren, 2014). Another approach could be to develop interventions and services tailored to specific at-risk populations. For example, in Canada an ongoing study aims to understand the feasibility of a brief psychoeducation program to reduce cannabis-related harm among undergraduate students promoting lower-risk cannabis use (Mader et al., 2020). The improvement of prevention and harm-reduction strategies, as well as an easier access to information on NPS, especially for individuals at a higher risk of misuse, could slow NPS diffusion and avert the consequences of substance use.

5. Conflict of Interest

- see title page -

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Table 1. Demographic characteristics of the sample.

Variables	**n**	**%**
total responders	1097	.
age		
mean (sd)	31.31 (9.81)	.
range	16-72	.
age class		
15-34	759	73.47%
35-64	266	25.75%
65	8	0.78%
gender		
Male	442	41.12%
Female	616	57.30%
Intersex	9	0.84%
no answer	8	0.74%
sexual orientation		
heterosexual	961	89.48%
homosexual	50	4.66%
bisexual	47	4.38%
other	3	0.28%
no answer	13	1.21%
nationality		
Italian	1044	97.84%
foreigners	17	1.59%
no answer	6	0.56%

parents' nationality		
both Italian	1017	95.31%
only father Italian	14	1.31%
only mother Italian	12	1.15%
both foreigners	17	1.59%
no answer	7	0.66%
housemate		
alone	197	18.67%
partner	248	23.51%
partner & sons	14	1.33%
sons	5	0.47%
family of origin	492	46.63%
friend	64	6.07%
flatmate	12	1.14%
other	5	0.47%
no answer	18	1.70%
house type		
own home	702	66.48%
rent house	303	28.69%
other	26	2.46%
no answer	25	2.37%
education		
primary school	2	0.19%
lower secondary school	41	3.94%
higher secondary school	352	33.81%

bachelor degree	141	13.54%
master degree	350	33.62%
post-graduate degree	144	13.83%
no answer	11	1.06%
work type		
independent/freelance	157	15.08%
employee	501	48.13%
student	299	28.72%
retired	8	0.77%
unemployed	41	3.94%
housewife	13	1.25%
other	4	0.38%
no answer	18	1.73%
monthly income		
<500 €	236	22.67%
501-1200 €	168	16.14%
1201-2300 €	371	35.64%
2301-4500 €	119	11.43%
4501- 6250 €	16	1.54%
>6251 €	12	1.15%
no answer	117	11.43%
nicotine consumption in the previous 6 months		
no	639	62.28%
yes	315	30.70%
no answer	72	7.02%

Cigarettes	219	
mean daily number	8.17 (6.68)	
Pipe	3	
mean daily number	1.00 (1.00)	
Cigars	10	
mean daily number	1.83 (1.33)	
Handmade cigarettes	119	
mean daily number	7.62 (5.73)	
alcohol in the previous 6 months		
no	143	13.94%
yes	861	83.92%
no answer	22	2.14%
Wine	671	
mean weekly number	3.05 (3.35)	
Beer	648	
mean weekly number	2.73 (3.13)	
Cocktails	357	
mean weekly number	1.74 (1.75)	
coffee		
no	118	11.70%
yes	880	87.22%
no answer	11	1.09%
mean weekly number	14.21 (9.13)	
tea		
no	329	32.61%

yes	641	63.53%
no answer	39	3.86%
mean weekly number	4.50 (3.52)	
energy drink		
no	873	86.85%
yes	65	6.47%
no answer	67	6.67%
mean weekly number	1.48 (1.17)	
ED access due to alcohol (lifetime)		
no	651	64.33%
yes	317	31.32%
no answer	44	4.35%
mean (sd) lifetime	4.73 (19.19)	
mean (sd) last 3 years	1.80 (16.74)	
lifetime contact with mental health professional		
no	518	52.69%
yes, at least 1 professional	445	45.27%
no answer	20	2.04%
child/adult psychiatrist	73	7.22%
psychologist	346	35.20%
speech therapist	34	3.46%

The responders for each variable may vary.

Table 2. Current use of NPS

variables	unadjusted OR [95%CI]	model 1 adjusted OR [95%CI]
age	0.99 [0.95 - 1.04]	-
gender		
female	(ref.)	(ref.)
male	**2.58 [1.12 - 5.98]**	1.60 [0.58 - 4.39]
intersexual	empty	empty
sexual orientation		
heterosexual	(ref.)	(ref.)
homosexual	**4.23 [1.38 - 13.12]**	3.16 [0.82 - 12.20]
bisexual	1.19 [0.16 - 9.12]	1.79 [0.22 - 14.48]
other	empty	empty
Italian nationality		
no	(ref.)	(ref.)
yes	**0.07 [0.01 - 0.28]**	**0.07 [0.01 - 0.37]**
parents' nationality		
both Italians	(ref.)	-
mixed	1.66 [0.21 - 12.83]	
both foreigners	3.81 [0.47 - 31.10]	
housemate		
alone	(ref.)	
partner	0.51 [0.16 - 1.63]	-
own family	empty	
sons	empty	
family of origin	0.35 [0.12 - 1.03]	

friends	1.75 [0.49 - 6.23]	
flatmate	2.38 [0.26 - 21.50]	
other	empty	
living condition		
own house	(ref.)	(ref.)
rented house	**3.52 [1.49 - 8.35]**	2.58 [0.97 - 6.90]
other	empty	empty
educational level		
lower secondary	(ref.)	
higher secondary	0.86 [0.11 - 7.02]	-
bachelor	0.23 [0.01 - 3.79]	
master	0.90 [0.11 - 7.33]	
postgraduate	0.03 [0.01 - 9.05]	
work		
independent	(ref.)	
employee	1.03 [0.33 - 3.19]	
student	0.69 [0.19 - 2.48]	-
retired	empty	
unemployed	empty	
homemaker	empty	
other	empty	
monthly income		
< 500€	(ref.)	-
501€-1200€	0.36 [0.04 - 3.22]	
1201€-2300€	1.71 [0.53 - 5.53]	

2301€-4500€ 4501€-6250€ >6251€	2.75 [0.72 - 10.46] empty empty	
alcohol - ED no yes	 (ref.) 2.17 [0.93 - 5.07]	-
substances - ED no yes	 (ref.) empty	-
psychiatric history no yes	 (ref.) 1.16 [0.52 - 2.61]	-
psychiatric history, relatives no yes	 (ref.) 1.13 [0.45 - 2.87]	-
nicotine consumption in the previous 6 months no yes	 (ref.) 2.27 [0.97 - 5.30]	-
binge alcohol in the previous 6 years no yes	 (ref.) **2.97 [1.20 - 7.36]**	 (ref.) 1.89 [0.69 - 5.17]
LR Chi^2 (p value)	-	0.0007

H-L Chi^2 (p value)	-	0.8029
M&Z pseudo-R^2	-	0.1671
BIC	-	200.431

Bold characters indicate a p-value < 0.05. 95%CI, 95% confidence interval; ED, Emergency department; BIC, Bayesian Information Criterion; H&L, Hosmer-Lemeshow; LR, Likelihood Ratio; M&Z, McKelvey and Zavoina; OR, Odds Ratio; ref, reference.

Table 3. Lifetime use of NPS.

Variables	unadjusted OR [95%CI]	model 1 adjusted OR [95%CI]
gender		
female	(ref.)	(ref.)
male	**2.50 [1.69 - 3.68]**	**2.33 [1.52 - 3.55]**
intersexual	empty	empty
sexual orientation		
heterosexual	(ref.)	(ref.)
homosexual	**2.63 [1.31 - 5.28]**	**2.52 [1.21 - 5.27]**
bisexual	1.94 [0.86 - 4.35]	1.47 [0.56 - 3.81]
other	3.51 [0.32 - 39.06]	4.12 [0.25 - 67.90]
Italian nationality		
no	(ref.)	-
yes	0.46 [0.12 - 1.72]	
parents' nationality		
both Italians	(ref.)	-
mixed	0.91 [0.27 - 3.11]	
both foreigners	0.64 [0.08 - 5.04]	
educational level		
lower secondary	(ref.)	-
higher secondary	0.47 [0.19 - 1.17]	
bachelor	0.86 [0.33 - 2.21]	
master	0.44 [0.18 - 1.09]	
postgraduate	0.72 [0.28 - 1.88]	
alcohol - ED		

no	(ref.)	(ref.)
yes	**3.62 [2.43 - 5.40]**	**3.38 [2.23 - 5.12]**
substances - ED		
no	(ref.)	-
yes	0.58 [0.07 - 4.55]	
psychiatric history		
no	(ref.)	(ref.)
yes	**1.52 [1.03 - 2.24]**	**1.58 [1.04 - 2.41]**
psychiatric history, relatives		-
no	(ref.)	
yes	1.06 [0.69 - 1.62]	
LR Chi^2 (p value)	-	0.0001
H-L Chi^2 (p value)	-	0.8091
M&Z pseudo-R^2	-	0.1653
BIC	-	650.481

Bold characters indicate a p-value < 0.05. 95%CI, 95% confidence interval; ED, Emergency department; BIC, Bayesian Information Criterion; H&L, Hosmer-Lemeshow; LR, Likelihood Ratio; M&Z, McKelvey and Zavoina; OR, Odds Ratio; ref, reference.

Table 4. Predicted probabilities, prevalence ratio and difference estimates comparing prevalence of use of NPS by use of emergency services due to alcohol.

	use of NPS, predicted probability		**use of ED due to alcohol**	
	no ED visit due to alcohol %	**ED visit due to alcohol %**	**prevalence ratio [95% CI]**	**prevalence difference [95% CI]**
Traditional drugs	4.0%	6.5%	1.63 [1.39 – 1.87]	0.25 [0.17 – 0.33]
NPS	8.7%	23.5%	2.70 [1.78 - 3.62]	14.8 [9.4 - 20.1]

95%CI, 95% confidence interval; ED, Emergency department.

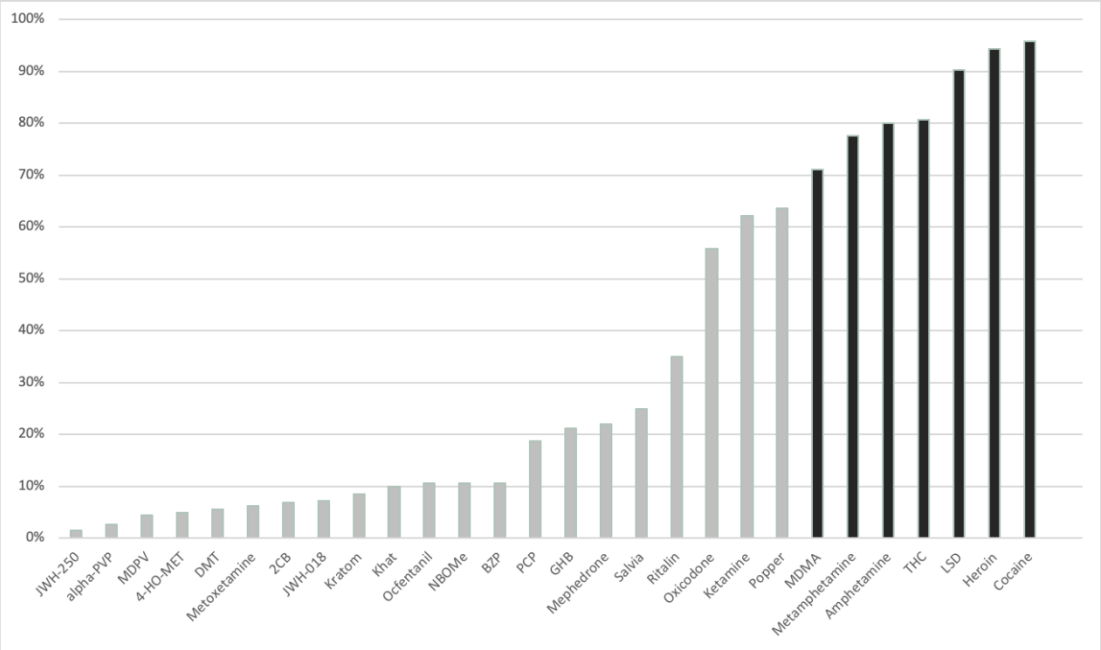

Figure 1 Knowledge on drugs of abuse. Black, traditional drugs; grey, NPS.

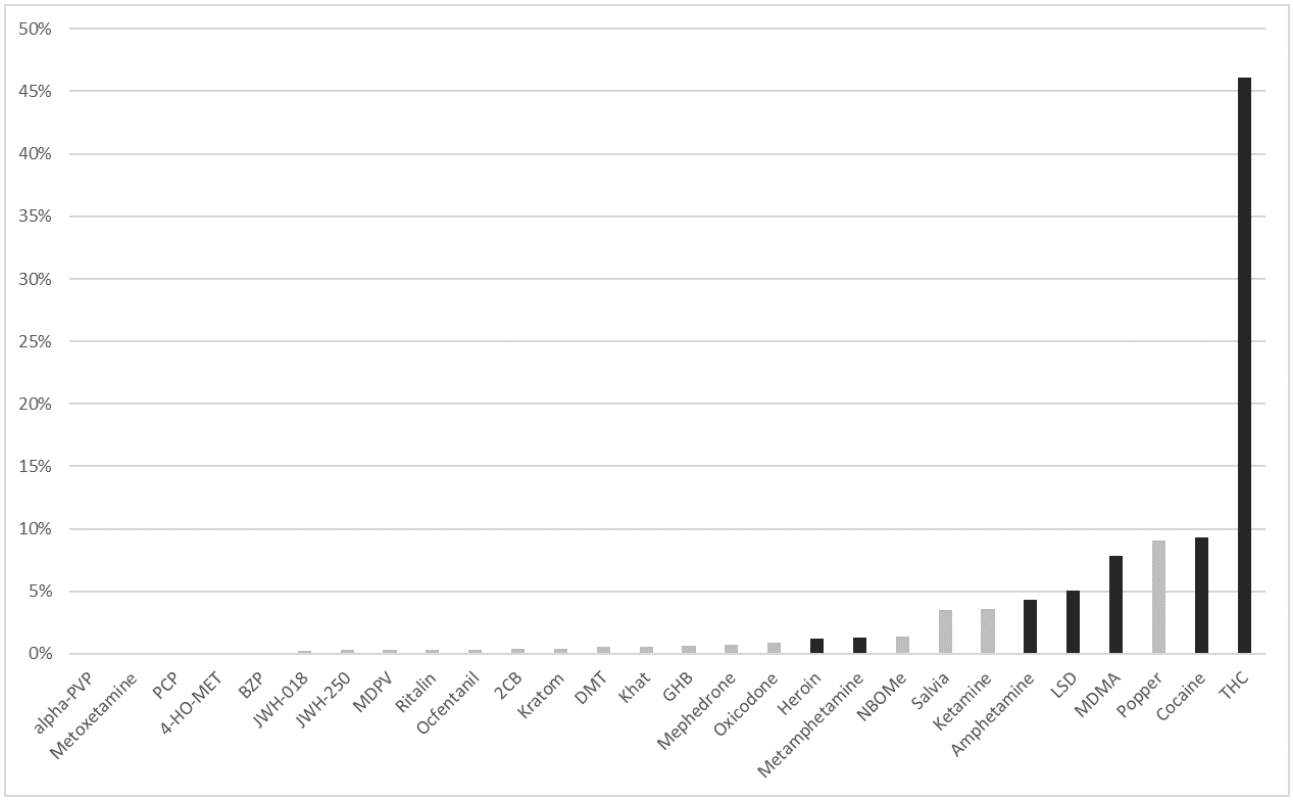

Figure 2 Lifetime use of substances of abuse. Black, traditional drug; grey, NPS.

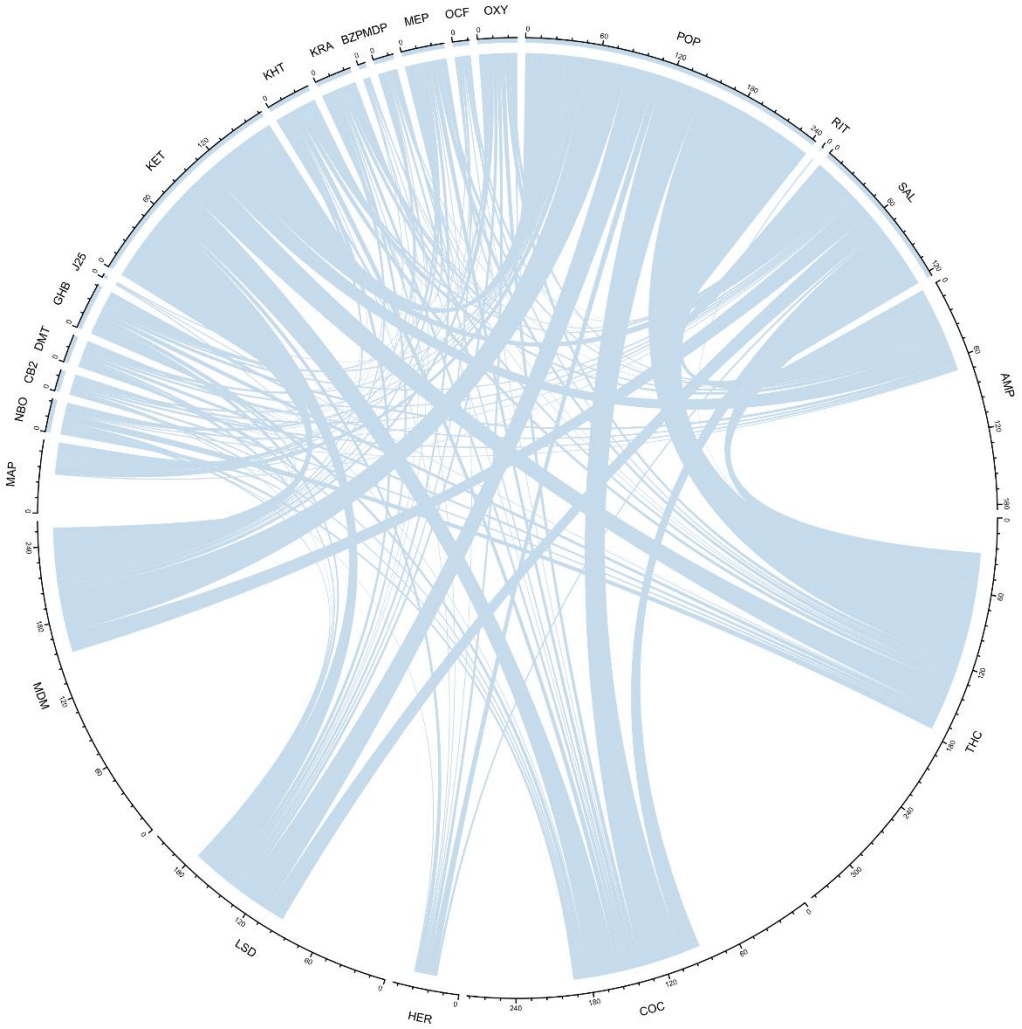

Figure 3 The chord diagram represents the co-occurrence of abuse of 2 drugs from questionnaires with an answer for all substances. AMP = amphetamine; BZP = benzylpiperazine; CB2 = 2CB; COC = cocaine; DMT = dimethyltryptamine; HER = heroine; KET = ketamine; KHT = khat; KRA = kratom; J25 = JWH250; MDM = MDMA; MAP = metamphetamine; MDP=MDPV; MET = 4-hydroxy-methylethyltryptamine; NBO = NBOMe; OCF = ocfentanyl; OXY = oxycodone; POP = popper; RIT = Ritalin; SAL = salvia.

APPENDIX 1

Table S1 Knowledge about drug purchase.

variables	n	%
where to find information		
friends	625	64.36%
family	140	14.42%
TV	673	69.31%
social network	432	44.49%
specialized blog	78	8.03%
internet	374	38.52%
specialized shop	26	2.68%
drug dealer	76	7.83%
no information	256	26.37%
where to buy drugs		
street/park	775	79.90%
discos	700	72.17%
friends	348	35.88%
family	13	1.34%
internet	313	32.29%
shop	146	15.05%
no information	121	12.47%

Demographic characteristics

1. *Age*: How old are you? _____
2. *Sex*: What sex are you?
    - M
    - F
    - I don't answer
3. *Nationality*: Are you Italian?
    - Yes
    - No
    - I don't answer
        - If no, where are you from? _____
4. Are your parents Italian?
    - Yes, both
    - Only father
    - Only mother
    - No
    - I don't answer
        - If not, where are they from? _____
5. *Living condition*: Who do you live with?
    - Alone
    - Parents / Family
    - Friends
    - Partner
    - Other_____
    - I do not answer
6. Is the house for rent or owned?
    - Rent
    - Home ownership
    - Guest
    - Other _____
    - I do not answer
7. *Education*: What is your highest school degree?
    - Primary school
    - Lower/Middle School
    - Higher secondary school
    - Bachelor's degree
    - Master's degree
    - Postgraduate degree
    - I do not answer
8. *Work*: What job do you do?
    - Unemployed
    - Employee
    - Independent Worker
    - Student
    - Other
    - I do not answer
9. What is your average monthly income (salary, loan from parents, scholarship, other ...)?
    - <500 euros
    - 501–1200 euros

- 1201 - 2300 euros
- 2301 - 4500 euros
- 4501 - 6250 euros
- > 6250 euros
- I don't answer

10. Which is the zip code of your city? _____

Life Habits

11. *Smoking:* referring to the last 6 months, are you a smoker?
    - Yes
    - No
    - I don't answer
12. What do you smoke?
    - Cigarettes
    - Pipa
    - Cigars
    - Tobacco
13. What amount (daily)? _____
14. *Alcohol:* referring to the last 6 months, do you drink alcohol?
    - Yes
    - No
    - I don't answer
15. What do you usually drink? (multiple choice possible)
    - Wine
    - Beer
    - Spirits
    - other: _____
16. What amount? (Indicate the number of glasses / drinks) _____
17. How often? (times / week) _____
18. Have you ever drunk so much that you did not remember part of the evening, loss consciousness or need help from a health professional (first aid, emergency department)?
    - Yes
    - No
    - I don't answer
        - If yes, how many times has it happened in your life? _____
        - If yes, how many times it has happened in the last 3 years? _____
19. *Coffee*: referring to the last 6 months, do you drink coffee (not barley coffee)?
    - Yes
    - No
        - if yes, in what quantity per week? _____
20. *Tea*: referring to the last 6 months, do you drink tea?
    - Yes
    - No
        - if yes, in what quantity per week? _____
21. *Energy drink:* do you drink energy drinks (eg Redbull, Monster, Burn ...)?
    - Yes
    - No
        - if yes, in what quantity per week? _____
22. *Sleep*: What time do you usually fall asleep at? _____

23. What time do you wake up? _____
24. How many hours do you sleep in total? _____
25. How do you consider the quality of your sleep? [1 to 4, with 1 "Worst" and 4 "Best"]
    - 1
    - 2
    - 3
    - 4

Mental Health History

26. Have you ever had contact with psychiatrists, psychologists, speech therapists or other services?
    - Psychiatrist
    - Psychologist
    - Speech therapist
    - No
    - Other_____
    - I do not answer
27. Have any of your family members ever had contact with mental health services?
    - Yes
    - No
    - I don't answer
28. Have you ever taken anxiolytics / benzodiazepines (eg Xanax, EN, Minias)?
    - Yes, now
    - Yes, in the past
    - No
    - I don't answer
29. Have you ever taken psychiatric drugs (antidepressants, antipsychotics, mood stabilizers)?
    - Yes, now
    - Yes, in the past
    - No
    - I don't answer
30. Have you ever taken natural / homeopathic substances with antidepressant, anxiolytic (eg hypericum, Bach flowers) properties?
    - Yes, now
    - Yes, in the past
    - No
    - I don't answer

Knowledge

31. Which of these substances you know (possible multiple answer):
    - THC
    - MDMA / Ecstasy
    - Cocaine
    - Heroin
    - Amphetamine / Speed
    - LSD
    - Popper
    - Ketamina / K / SpecialK / Kitkat / SuperK
    - Mephedrone / Meow-meow / Mafalda / Top cat (cathinones)

- Alfa-PVP / Flakka (cathinones)
- GHB
- JWH-018 / Spice (synthetic cannabinoids)
- JWH-250 (cannabinoid-synthetic)
- BZP / Jax / A2 / Legal X / Flying Angel (piperazine)
- PCP / Angeldust / (phencyclidine)
- 2C-B (phenethylamines)
- 25i-NBOMe (phenethylamines)
- 5-HO-DMT / DMT (tryptamines)
- 4-HO-MET (tryptamines)
- Salvia divinorum / Maria Pastora / Magic Mint / Erba Pastora
- Khat
- Kratom / Ketum / Kakuan / Thom
- Ritalin
- Relevin ***
- I do not answer

32. Where did you hear about these substances or where did you look for information about them? (multiple choice possible)
    - friends
    - Family
    - Television
    - Social Network
    - specialized blogs
    - Internet Search
    - specialized shops
    - Sellers of illegal substances
    - I do not answer
33. According to your experience, where do you buy these substances? (multiple choice possible)
    - Route / park
    - In the disco / meeting places
    - Friends
    - family members
    - the Internet
    - Specialized stores
    - Other_____
    - I do not answer

Use

34. Which of these substances did you use? (multiple choice possible)
    - Substances listed above
    - I don't answer
        - For each Yes, sub-question: Currently or in the past? How often?
35. Have you ever had one of these symptoms concomitantly with substance use?
    - Nausea
    - Headache
    - Vertigo
    - Tachycardia
    - Tremors
    - Involuntary muscle spasms / movements

- Anxiety
- Insomnia
- Loss of memory, amnesia
- Paranoia
- feeling of being "out of your body"
- Disturbed vision
- Muscular or bone pain
- Breathing difficulties
- Flushing sensation
- I don't answer
    - For every effect: with what substance? How many times: once, sometimes, every time I take the substance.

36. Have you ever taken a substance without knowing what it was?
    - Yes
    - No
    - I don't answer
        - If yes, how many times has it happened? _____
37. Have you ever needed medical assistance (Emergency medical service) following the use of some substance of abuse (alcohol excluded)?
    - Yes
    - No
    - I don't answer
        - If yes, how many times?