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Seizures of New Psychoactive Substances on the Italian territory during the COVID-19 pandemic

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ABSTRACT

In recent years, the availability and the consequent consumption of New Psychoactive Substances (NPS) have proliferated at an unprecedented rate, posing a significant risk to the public health and challenging the law enforcement efforts to tackle the black market. In particular, large availability on Internet and unmonitored shipping have facilitated the diffusion of NPS on national territories. In this scenario, the forensic activity based on the process of drug detection, including investigation, seizure, recognition and analytical identification is crucial to get insights into the drug black market transformation. In this study, we describe the results obtained from the analysis of hundreds of packages seized during the months of year 2020, and suspected to contain NPS because not reacting with standard field test kits. We focused on the analysis by GC-MS and HPLC-HRMS, and NPS in particular, trying to underline the most common molecules present on the Italian territory during the COVID-19 pandemic. NPS were identified in 92.6% of the samples. The most prevalent compounds were synthetic cathinones, and 3-MMC in particular, which alone accounted for 18.6% of the total cases. Other prevalent molecules were 5F-MDMB-PICA, 2-FDCK, 1cp-LSD and 1P-LSD. Fentanyl was never detected. The information obtained from drug seizures is crucial to publish national alerts, which are in turn important to assist the legislative effort to ban new compounds and the update of toxicological and analytical methods.

KEYWORDS

New Psychoactive Substances, NPS, cathinones, seizure, black market

INTRODUCTION

New psychoactive substances (NPS) are designer drugs which have progressively become a global issue, with over 100 countries and regions throughout the world having reported the emergence of NPS [1,2]. In recent years, the availability and the consequent consumption of NPS have proliferated at an unprecedented rate, posing a significant risk to public health and challenging the law enforcement efforts to tackle the black market. In particular, large availability on the Internet and unmonitored shipping have facilitated the diffusion of NPS on national territories. While in the initial phases of the phenomenon the term “new” or “novel” did not necessarily refer to new

substances but instead to substances that have become available in the illicit market, today the introduction on the market of hundreds of newly synthesized compounds is commonly observed. Among these substances, synthetic cannabinoids, synthetic cathinones, phenethylamines, piperazines, and tryptamines have been the most popular [3]. Nevertheless, more recently, there has been an emergence of new synthetic opioids [4,5] and designer benzodiazepine derivatives [6]. In particular, clandestine laboratories have caused rapid proliferation of novel substances in recent years, thus making their detection potentially demanding in different contexts, such as forensic drug chemistry and analytical toxicology. Given the numerous possibilities of altering structures of chemicals, the number of NPS is continuously increasing and, as a result, they may pose serious challenges to researchers and policymakers that try to assess the risk of harm and to take appropriate measures to control them [7].

In attempting to establish the identity of a controlled drug in suspect material, several analytical approaches have been proposed, including nuclear magnetic resonance spectroscopy [8], gas chromatography-mass spectrometry (GC-MS) [9], ion mobility spectrometry [10], thin layer chromatography [11], liquid chromatography coupled to high-resolution mass-spectrometry (LC-HRMS) [12], liquid chromatography-mass spectrometry with time of flight detection [13] and Raman spectroscopy [14]. However, when a novel or unknown NPS is suspected to be present in a seized sample, mass spectrometry can play a pivotal role [15].

The main factors that are posing various problems to the agencies working at different levels of the process of drug detection, including investigation, recognition and analytical identification, include i) NPS are not homogeneous and somehow ambiguous legal status, ii) the rapid and transient presence of NPS in the market, iii) the fact that NPS are often disguised in mixed composition, and iv) are traded/trafficked in small quantities in unsuspected packaging (sold over the Internet and sent by post) [16]. Great flexibility in legislative approaches exists at the regional and the national levels [17]. Generic legislations have aimed to control both individual NPS and other have aimed to ban any group of substances with structural similarities [18]. In Italy, various decrees were issued in the last ten years in order to update the list of controlled psychotropic substances: chemical substances are not just cited name by name, but also as groups of structurally related analogues, such as those compounds derived from 3-phenyl acetylindole, the structures analogous to 3-(1-naphthoyl)indole, 3-benzoylindole and the ones derived from 2-amino-1-phenyl-1-propanone [19].

In this manuscript, we describe the results obtained from the analysis of hundreds of seized packages, suspected to contain NPS. The samples were obtained from law enforcement seizures of shipped packages during the months of year 2020. The current outbreak of severe respiratory disease, COVID-19, has profoundly changed the lives of many people all over the world, being especially difficult on those individuals already vulnerable, including users of illegal drugs [20]. Very scarce evidence-based data on such effects on drug diffusion during the COVID-19 pandemic have been published so far therefore, we focused on the identification of NPS, trying to underline the most common NPS present on the Italian territory.

MATERIALS AND METHODS

Seizure Samples

The investigation focused on samples allegedly containing NPS because not reacting with standard field test kits for common drugs of abuse. 479 drug samples taken from 212 seized postal parcels collected during investigative operations by the Scientific Investigation Unit of Carabinieri (R.I.S.), between May and October 2020, were analyzed by GC-MS and LC-HRMS. The seized substances were sent by post in specially sealed containers or envelopes so that their contents could be masked. In this scenario NPS represent about 92% of the total number of seizures carried out by checking postal parcel between May and October 2020.

Since these samples are connected to criminal activity, no further information such as location and exact data collection are available.

Gas chromatography – mass spectrometry

Each seized sample (<50mg) was dissolved in 10 ml of methanol (Honeywell, ACS Reagent, Pur. $\geq 99,8\%$), sonicated in an ultrasound bath at room temperature and then, 1 ml of solution was transferred to 2 mL vials. Analysis was performed using an Agilent 7890B gas chromatograph equipped with a quadrupole mass-selective detector (MSD) Agilent Technologies 5977B. The MSD was operated in the electron ionization (EI) mode, with an ionization potential of 70 eV, a scan range of 25-600 amu. The GC was fitted with a 30m x 0.25 mm ID fused-silica capillary column coated with 0.25 μm 5% diphenyl 95 % dimethylpolysiloxane stationary phase (HP5-MS). The oven temperature was programmed as follows: initial temperature 80 °C, initial hold 2 min, program rate 25°C/min up to 280°C, held for 15 min. Column flow was 1,2 mL/min. The injector was operated in the split mode (5:1) at 260°C. The injection volume was 1 μl and total run time was 20 min.

Only for the identification of 5F-Cumyl-Pegacalone, the oven temperature was programmed as follows: initial temperature 80 °C, initial hold 3 min, program rate 10°C/min up to 280°C, held for 25 min. then ramped at 10°C/min up to 300°C, and finally maintained for 30 min. Column flow was 2 mL/min. The injector was operated in the split mode (5:1) at 260°C. The injection volume was 1 μl and total run time was 80 min. Substances identification was performed by the comparison with the data in the library, we used the potential of the Mass Hunter software provided by Agilent Technologies. By selecting the chromatographic peak of the sample, it is possible to investigate the relative mass spectrum, the software then allows to connect to the libraries mentioned above and to view any correspondences present on SWGDRUG 3.8, ENFSI 2018, Wiley 7 and Cayman library on the same mass spectrum. As concern the EMCDDA database, it was consulted manually, by investigating the fragmentation pattern.

The presented GC-MS method proved to be insufficient in the identification of LSD and its derivatives, 1cP-LSD and 1P-LSD. The chromatogram obtained from the analysis of those samples showed no signals that could lead to the presence of substances mentioned. For this reason, it was decided to include the analysis performed with a different technique, in particular LC-HRMS.

The analyses were carried out using an already validated untargeted method for the determination of NPS [21] while the search of the target compounds was performed by evaluating

the extracted current ion (XIC) of the analyte from the total ion current (TIC) registered in Fullscan-data dependent. By isolating the compound of interest, it was possible to appreciate its fragmentation pattern and, as described in the following paragraph (LC – HRMS Analysis), they were then compared with the data present in the mzCloud and HighResNPS libraries in order to give a certain identification of the compound.

All seized material were subsequently analyzed in LC-HRMS with the aim of inserting our spectra in the HighResNPS library.

LC–HRMS Analysis

Seized samples were stored at room temperature until extraction, then 1 mg of seizure was extracted with 1 mL of methanol, vortexed for 1 min, sonicated at 25°C for 10 min and finally filtered through a 0.22 µm nylon filter from Agilent (Santa Clara, CA, USA). The obtained extracts were diluted 1: 10000 and subsequently 5 µL were injected into the UHPLC system. The seizures extracts were analyzed by HPLC–HRMS, using a previously published method [21].

Identification of mass spectra was performed using different public libraries, mzCloud (www.mzcloud.org/) and HighResNPS [22]. To confirm the presence of the substances in the seizures, a comparison of the high-resolution mass spectra obtained from the analyzes with those present in these libraries was executed. Despite it is the greater time-consuming step, in the data analyses process, MS/MS spectral search is usually manually performed, as usual. In this way it was possible to base the identification on multistage MS spectral trees contained in mzCloud library, and thanks to the data inserted in the library, it is also possible to correlate a hypothesis of structure of the fragment to each signal of the fragmentation pattern. On the other hand, using HighResNPS it is possible to base the identification by means of the comparison with spectra obtained by different active users. The strength of this libraries lies in its continuous updating, and in the ease with which it is possible to consult and download the information needed. Regarding the comparison of mass spectra with the HighResNPS library, it was conducted online. The comparison was performed focusing on the accurate mass of the molecular ion. When dealing with structural isomers, characteristic fragmentations of the compounds that were assumed to be present were sought. Although the collision energies used are sometimes different from those declared in the library, in all cases it was possible to recognize the typical fragmentation pattern of the molecule.

RESULTS

A total of 479 samples obtained from 212 seized postal parcels was analyzed. The samples were seized between May 2020 and October 2020 and presented as powders, crystals, tablets and liquids. Only seven samples were not labelled; among the remaining 472 samples, the molecule identified by the analyses matched what was labelled on the package in 460 items, leaving an incongruity to only 12 pieces. Among the 479 samples, the analysis revealed the presence of an alleged psychoactive substance in 444 items (92.6%), of a pharmaceutical drug (6.5%) in 31 items and of a cutting agent (0.8%) only in 4 items.

The identified compounds were attributable to 46 structures, with the most common being synthetic cathinones. Of the 46 molecules, 37 were considered as NPS and 9 as pharmaceuticals or doping agents. Of the 37 NPS, only 16 are scheduled according to the Italian Legislation, while 21 were non-scheduled structural analogs. Quite impressively, 35 molecules out of 46 have been never reported in Italy before 2020 [23]. Unfortunately, some sections of the EMCDDA website are reserved only for registered users who are part of the Italian EWS also known as Sistema Nazionale Allerta Precoce (SNAP). For all users, the Istituto Superiore di Sanità (ISS) annually draws up a report to inform about the published data in the EMCDDA website. Among the 7 pharmaceuticals or doping agents, only two are scheduled from the Ministry of Health in a specific table, while the remaining five were non approved substances.

In the majority of seized parcels (94%), only one active compound was detected; in the remaining 6%, two, three or up to seven different molecules were identified in the same sample.

Figure 1 depicts the frequency of items for each NPS encountered, classified according to the categories they belong to. In Figure 1, NPS are classified as suggested by EMCDDA classification. The 37 identified different molecules were distributed as follows: 8 synthetic cathinones, 5 synthetic cannabinoids, and 24 miscellaneous substances including less prevalent NPS classes (6 arylcyclohexylamines, 4 phenethylamines, 2 piperidines, 7 tryptamines, 3 derived from amphetamines, 1 benzothiadiazine, 1 analog of phenmetrazine). In Figure 2, an itemized representation of the most commonly found NPS is shown.

SYNTHETIC CATHINONES

Cathinones were the most frequently seized substances, having contributed to 117 items (24.4% of the total seizure). In particular, the meta-isomer of mephedrone 3-MMC was the most recurrent (89 items, 76% of the total seized cathinones), followed by N-ethylhexedrone (15 items, 13% of the total seized cathinones). Sporadic findings included 4-Cl-PVP, 4-CMC, α -PHiP, eutylone, BMDP, and MDPHP.

SYNTHETIC CANNABINOIDS

The detection of synthetic cannabinoids contributed to 7% (34 items) of the total number, with 5 different cannabinoids encountered. The most common compound was 5F-MDMB-PICA (27 items, 79% of the total seized synthetic cannabinoids). Other sporadic findings included 4F-MDMB-BICA, 4F-MDMB-BINACA, 5F-Cumyl-PeGACLONE, and MDMB-4en-PINACA.

MISCELLANEOUS NPS

Other findings included i) arylcyclohexylamines, among which the most common were 2-fluorodeschloroketamine (19 items) and methoxpropamine (10 items); ii) phenethylamines, among which the most common were the 2 and 3 isomers of FEA (17 items) and the 2 and 3 isomers of FMA (11 items); iii) tryptamines, among which the most common were 1cp-LSD (53 items) and 1P-LSD (31 items). It is noteworthy the high number of items identified to contain either 1cp-LSD or 1P-LSD. The two molecules together combined for almost the 18% of the total seizure.

DISCUSSION AND CONCLUSIONS

During the COVID-19 pandemic, a decrease in the demand of stimulants was observed due to the inaccessibility of usual recreational settings, while alternative substances and NPS have likely proliferated [24]. The analysis of illicit drug seizures is a useful indicator to reflect prevalence of different molecules in the black market and among drug users. In particular, this information can shed light on the most common drugs in certain periods and in certain territories, thus assisting the activity of all subjects involved in forensic investigation related to drug traffic and use. For example, toxicological laboratories will use the information from seized samples to have up-to-date targeted analytical methods on biological samples. Special attention is to be paid since NPS seizures have increased in Europe in the last decade [25] and they are not completely controlled by local authorities.

In our study, we observed a large diffusion of several NPS from different structural classes. In the large majority of samples, only one drug was detected, thus reducing the risk of unaware poly-abuse for users. Synthetic cathinones were the most prevalent NPS, accounting for a quarter of all seizures. Our finding probably reflect the overall demand for stimulants, with many of them used as replacements for MDMA [26]. Quite remarkably, the second most frequently encountered compounds belonged to the class of tryptamines, while available data on number and categories of substances reported to the EU early warning system show higher prevalence for other groups of compounds [25]. Similarly to what was previously shown by other investigations on the Italian situation [19], our findings showed the presence of a wide number of NPS, including substances not controlled by the Italian criminal law. Overall, the most prevalent compounds were 3-MMC, 5F-MDMB-PICA, 2-FDCK, 1cp-LSD and 1P-LSD. While synthetic cathinones are well known to be common, the latter two were not detected in previous studies [19, 27]. While several pharmaceuticals, mostly benzodiazepines, were observed, it is noteworthy that fentanyl, or more in general novel synthetic opioids, were never detected.

Postal parcel tracking is crucial to intercept illicit drugs and investigate the black market. Drug traffickers and drug users are frequently using postal service to transfer illicit molecules, and NPS in particular, which represent a serious warning to public health. Trafficking often includes non-scheduled substances, possibly in order to avoid sanctions, insomuch that the real content of the parcel is often disclosed on the package. As a matter of fact, in our study we observed that the molecule identified by the analyses matched what was labelled on the package in the large majority of cases. More remarkably, we found an impressive number of molecules which were reported for the first time on the Italian territory. Therefore, we were able to inform the National Early Warning System, allowing the collection and the prompt reporting of information on the appearance of NPS at national level. During the COVID-19 pandemic, it is plausible that i) border closures may have disrupted the substance supply, ii) lock-downed people who use drugs have looked for alternative suppliers, namely the postal service. For many, these changes have likely led to a substitution of drugs present on national territories.

The variety of identified chemical structures, often not yet scheduled in Italy, does certainly serves as enlightening example of the rapid pace by which manufacturers can produce and supply new drugs to circumvent drug laws. In this scenario, an effective, sensitive and selective strategy

capable of discriminating among different NPS with diverse chemical structures is deemed strategic to challenge the NPS phenomenon. Laboratories in particular can take advantage of existing technological resources in order to provide up-to-date information to other subjects involved, law enforcement and policy makers *in primis*.

In conclusion, it is essential to use the information obtained from drug seizures to publish national alerts and thus assist other sectors, such as the legislation (i.e., to ban the newly identified molecules) and the laboratories performing toxicological analyses.

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Figures

Figure 1 Classification of seized NPS based on EMCDDA classification.

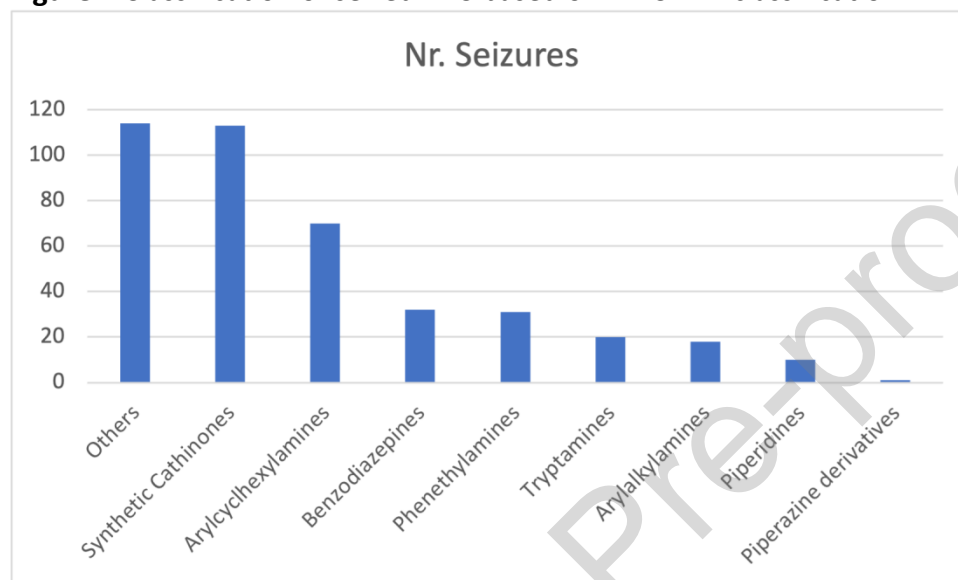
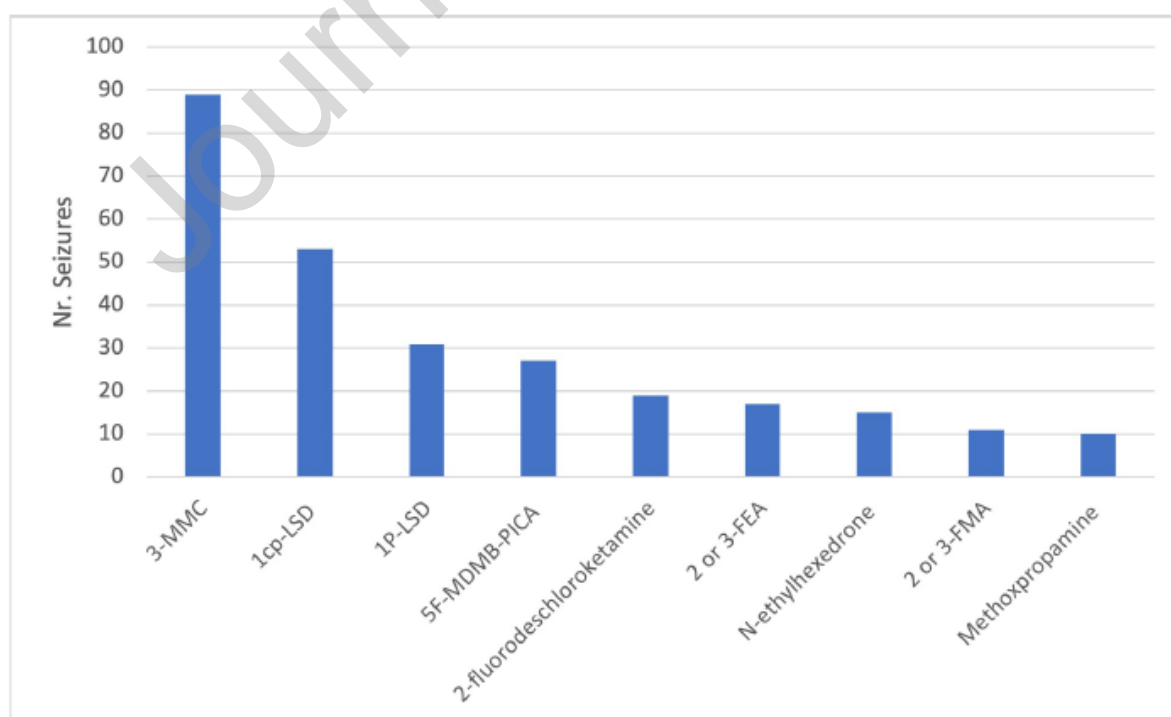


Figure 2 Itemized list of the most detected NPS



Highlights

- Drug traffickers and drug users are frequently using the postal service to transfer illicit molecules, and NPS in particular
- We focused on the identification of the most commonly seized NPS during the COVID-19 pandemic
- A large variety of NPS was identified, with synthetic cathinones being the most popular
- The information obtained from drug seizures is crucial to publish national alerts and to update toxicological methods

Author statement

Alberto Salomone and Adolfo Gregori: Conceptualization and Supervision; Flaminia Vincenti: Data curation; Martina Flammini and Fabiana Di Rosa: Formal analysis; Flaminia Vincenti, Alberto Salomone and Adolfo Gregori: Writing - original draft; Writing - review & editing.

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