

The complex and constantly evolving public health threat of new psychoactive substances in Italy: addressing the main functions of a national observatory of drugs

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Abstract

At the end of the 90s in Europe, the new psychoactive substances (NPS) phenomenon was limited to a small number of molecules created to mimic the actions and psychoactive effects of licensed medicines and existing drugs that are controlled by the United Nations drug conventions and therefore traded as their “legal” replacements. NPS were mostly circulating in rave parties and electronic music festivals. The globalization, the evolution of e-commerce and the growing popularity of NPS, facilitated the development of a wide illegal market in constant expansion. The dynamic nature of this phenomenon has led to an evolution in the prevention and monitoring of NPS trafficking within the European Union. The European legislative system has been amended with the aim of creating a faster and more effective regulatory system to tackle NPS diffusion and ban their sale and circulation. At the end of 2008, in compliance with the European Council Decision 2005/387/JHA, the Anti-Drug Policies Department of the Presidency of the Council of Ministers activated the National Early Warning System to promote a rapid exchange of information on NPS between Italy and the EU.

Key words

- NPS
- early warning system
- Italy
- psychoactive drug

INTRODUCTION

New psychoactive substances (NPS) are drugs that are not controlled by the United Nations international drug control conventions of 1961 and 1971 but may pose similar threats to public health [1]. At the end of the 90s in Europe, the NPS phenomenon was limited to a small number of molecules traded as “legal” replacements for the controlled drugs (such as cannabis, heroin, benzodiazepines, cocaine, amphetamines, and 3,4-methylenedioxymethamphetamine – MDMA), and were mostly circulating in rave parties and electronic music festivals.

The globalization, the evolution of e-commerce and

the growing popularity of NPS, which were not expressly prohibited at the time, facilitated the development of a wide illegal market in constant expansion. In less than twenty years, NPS production and sale increased exponentially: at the end of 2019, the European Monitoring Center for Drugs and Drug Addiction (EMCDDA) had reported approximately 790 NPSs circulating throughout Europe, 53 of which were identified for the first time that year [2].

Many NPS were originally developed as therapeutic drug candidates and/or as pharmacological tools to investigate endogenous systems of the body, although none of them were clinically tested [3]. For example,

the synthetic cannabinoids were originally developed to provide insights into the endocannabinoid system and help develop new medicines [4, 5]. The majority of NPS, however, were specifically synthesized for recreational use. Due to the absence of experimental and clinical data of NPS, pharmacological and toxicological data are rarely available [6-9]. Therefore, NPS use may induce unknown and unexpected effects, including acute and chronic toxic effects, as reported in numerous cases of intoxication and deaths in Europe and abroad [10].

Clinical similarities exist between NPS classes and the more established illicit substances they are intended to mimic. These similarities are assumed on the basis of their similar chemical structure and pharmacological actions. However, their harms can be qualitatively more serious, and sometimes different from those produced by controlled drugs. Moreover, some NPS such as fentanyl derivatives and synthetic cannabinoids, show high potency that make easier to unintentionally overdose.

Little is currently known about the chronic harms of NPS use. There is emerging evidence that synthetic cannabinoids might be associated with more rapid onset of dependence and a more complex withdrawal syndrome than is cannabis [11]. Risk of dependence and withdrawal has also been noted with some stimulant NPS [12].

Despite the recent efforts towards NPS control, most of these substances are still legal in many countries, hindering the combat against drug trafficking and exposing oblivious consumers to potential health risks [13, 14]. At any times, new molecules are ready to be introduced onto the market, both to satisfy the consumer demands and to evade international ban. The NPS phenomenon therefore represents a serious, complex, and constantly evolving public health threat [15-17]. New challenges related to the growing number of highly potent substances, like synthetic cannabinoids, new synthetic opioids and fentanyl analogues, which have been responsible for explosive outbreaks, have emerged [18-21].

Over the years, the dynamic nature of the NPS phenomenon has led to an evolution in the prevention and monitoring of NPS trafficking within the European Union (EU). The European legislative system has been amended with the aim of creating a faster and more effective regulatory system to tackle NPS diffusion and ban their sale and circulation [22].

THE EUROPEAN EARLY WARNING SYSTEM (EU EWS)

In 1997, on a proposal from the EU Council, an early warning system (EWS) was implemented in Europe for the rapid exchange of information on NPS between EU Member States, to rapidly detect, assess, and respond to health and social threats (97/396/DJHA). The EWS was characterized by a regulatory structure organized in three phases: 1) the early warning of Member States upon the identification of new NPS in Europe, 2) the assessment of the risk associated with their consumption, and 3) the rapid implementation of control measures. The EMCDDA was responsible for the application of the first two phases.

However, this strategy needed to evolve to keep up with the spread of NPS. With the Framework Decision of May 10, 2005 (2005/387/JHA), the European Council established the current European EWS, coordinated by the EMCDDA in close collaboration with Europol and its law enforcement networks, the European Medicines Agency (EMA), the European Commission, the European Center for Disease Prevention and Control (ECDC), the European Chemicals Agency (ECHA), and the European Authority for Food Safety (EFSA). The European Commission is responsible for proposing control measures. The European Council also instructed all EU Member States to implement similar EWS to build a solid network for collecting, analyzing, assessing, and communicating the data on NPS throughout Europe. To date, the EWS includes 30 national EWS (28 EU Member States, Turkey, and Norway). The organization and functioning of the national early warning systems is a national responsibility. While these systems have developed to meet national needs, they draw on a common format and guidelines to report information to the EMCDDA. EWS guidelines and Risk Assessment Guidelines have been developed in 2007 and 2010 respectively, to provide the rationale, steps, procedures, roles, and responsibilities for the operation of the EU EWS. In January 2020 EWS guidelines have been updated to reflect the requirements of the new legislative package with respect to information exchange and the early warning system [23]. New Risk Assessment guidelines have been updated and published in December 2020 [24].

THE ITALIAN EARLY WARNING SYSTEM

At the end of 2008, in compliance with the European Council Decision 2005/387/JHA, the Anti-Drug Policies Department (Dipartimento per le Politiche Antidroga, DPA) of the Presidency of the Council of Ministers (PCM) activated the National EWS (Sistema Nazionale di Allerta Precoce, SNAP) to promote a rapid exchange of information on NPS between Italy and the EU.

In June 2016, the DPA designated the National Center for Addiction and Doping (CNDD) of the Istituto Superiore di Sanità (ISS) to organize and manage SNAP. The CNDD-ISS is supported by the Poison Center of the Maugeri Scientific Clinical Institutes of Pavia (CAV-PV) to manage NPS clinical and toxicological aspects, the Research Unit of Forensic Toxicology of the Sapienza University of Rome (FT-UNIROME1) to manage biotoxicological and analytical/technical aspects, and the Central Antidrug Service (Direzione Centrale per i Servizi Antidroga, DCSA) to ensure law enforcement. SNAP also involves Collaborative Centers across the country, such as law enforcement agencies and their laboratory networks, analytical toxicology laboratories, forensic toxicology laboratories, poison centers, health and care systems, universities and research institutes, medicines regulatory authorities.

SNAP follows and integrates the three regulatory phases of the EU EWS. When a NPS is first identified in Europe, SNAP is informed through a detailed report from EMCDDA and relays the information to the

national network. Conversely, all the reports on NPS circulating in Italy, which are collected by the national network of Collaborative Centers, are conveyed to the CNDD-ISS, the three support units, and the DPA, which relays the information to the EMCDDA. This system allows the EU and national EWS networks to detect and assess any potential threats, and identify and implement any response measures that might be required.

Phase 1 – Early warning

The early warning phase involves an input information flow and an output information flow managed by the CNDD-ISS and its three support units. The input flow includes the reports on the identification of NPS in Europe, from the EMCDDA, and in Italy, from the Collaborative Centers, based on seizures and/or acute intoxication and/or deaths.

These reports are supported by laboratory and analytical data (e.g., chromatograms and mass spectra) of the NPSs identified in seizures (e.g., powders, tablets, tablets, herbal preparations) or biological samples (e.g., blood, serum, urine, hair) and by other any available information.

The CNDD-ISS developed a new online platform to facilitate the contribution to the network by individual collaborative centers [snap.iss.it]. This system simplifies and harmonizes the collection of NPS data in Italy, optimizing the reporting activity. Moreover, it collects all the reports concerning NPS identified in Europe from the EMCDDA. An internal database archives chemical and analytical data of more than 600 NPS.

The data from the input flow are verified and supervised by the CNDD-ISS, in collaboration with CAV-PV and of the FT-UNIROME1

Specific informative documents are thereafter produced about NPS reported in the EU from the EMCDDA and in Italy from the Collaborative Centers. These

documents represent the output information flow, supervised and approved by the DPA, and are sent to all the Collaborative Centers and to specific departments of the Ministry of Health to keep them constantly updated on the NPS circulating in the EU and on the national territory.

From June 2016 to June 2020, the SNAP received almost 590 reports from the EMCDDA and the network of Collaborative Centers. About 62% of these reports concerned 169 NPS circulating in Italy and reported by the Collaborative Centers network during the considered period (Figure 1). The number of new substances reported has increased each year reflecting the growth in the NPS market. It may also reflect the increasing contribution by individual Collaborative Centers, especially law enforcement agencies, toxicology laboratories and poison centers, in reporting NPS detection to the SNAP. The drop in 2020 may reflect the impact of the response measures, such as the closure of public spaces and “stay-at-home” measures, related to the coronavirus disease (COVID-19) pandemic [15, 16]. These 169 NPS belong to different classes of compounds such as synthetic cannabinoids, synthetic cathinones, phenethylamines, synthetic opioids, tryptamines, arylalkylamines, benzodiazepines, piperazines, and plants. During the considered period, the most representative classes were synthetic cathinones (28%), synthetic cannabinoids (14%), and synthetic opioids (12%) (Figure 2). These findings are concordant with NPS data from the EU EWS network and reported annually from the EMCDDA. From 2007 to the end of 2018, the EMCDDA was monitoring 190 synthetic cannabinoids, 138 synthetic cathinones and 49 synthetic opioids [25].

Synthetic cathinones are typically sold as legal replacements for controlled stimulants such as amphetamine, cocaine, and MDMA [26, 27]. They act on the central nervous system with sympathomimetic effects

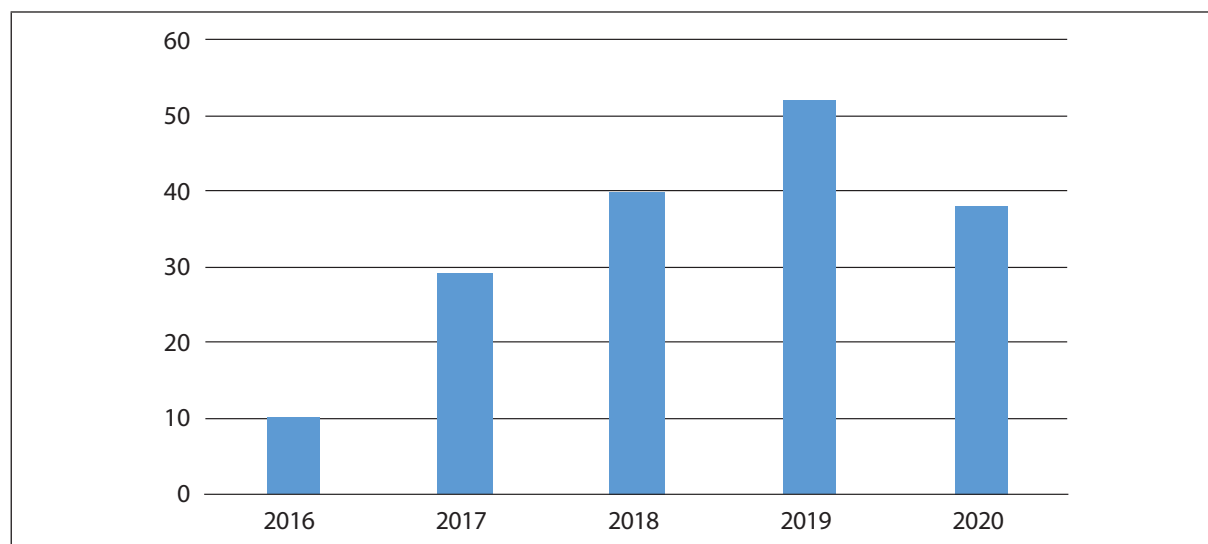


Figure 1 Number of NPS (new psychoactive substances) identified in Italy by the Collaborative Centers network by year (June 2016 – June 2020).

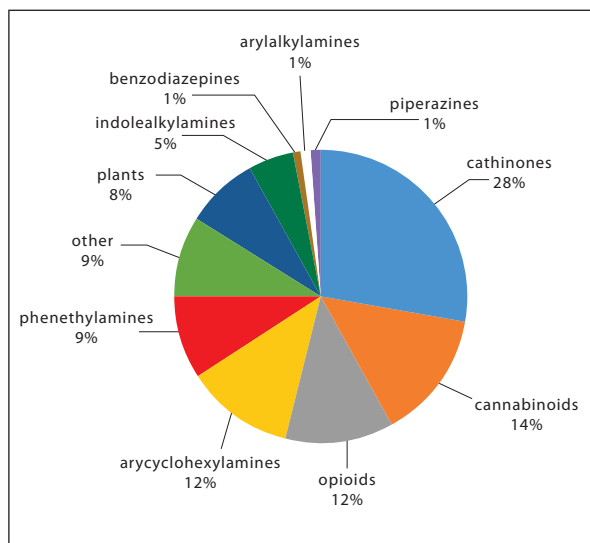


Figure 2
Chemical classes of the 169 NPS (new psychoactive substances) identified in Italy by reporting activity of the Collaborative Centers network.

(i.e., hallucinations, overstimulation) similar to those occurring after cocaine or amphetamine overdose. Generally the cathinones are used recreationally; however they are also used by high-risk drug users, including people using stimulants and/or heroin and other opioids [28]. In Italy, synthetic cathinones were identified both in seized sample from law enforcement and in biological samples of intoxicated users, mephedrone, MDPHP, α -PVP, α -PHP, 3-MMC, and eutylone being the most frequently reported. Increased availability and harms associated with synthetic cathinones have been reported by several EU countries (i.e., Belgium, Netherland, Latvia) [29]. Synthetic cannabinoids are sold also as legal replacement for cannabis. Generally, they are sprayed on herbal plant material and smoked [30, 31]. They act on the same brain cell receptors as tetrahydrocannabinol (THC). However, synthetic cannabinoids may affect the brain in different and unpredictable ways: people who smoke these products can react with rapid heart rate, vomiting, agitation, confusion, and hallucinations. Their high potency can pose a high risk of severe poisoning that can also be fatal. In Italy, synthetic cannabinoids were identified mostly in samples seized by law enforcement, and to a lesser extent, in biological samples of intoxicated users. Over the last year France, Germany, Swiss and the Netherlands reported samples of cannabis contain low level of THC and synthetic cannabinoids. In France these detections have been associated with “light intoxications” [29]. Synthetic opioids, and in particular fentanyl and fentanyl derivatives, are sold as legal replacement for controlled opioids, such as heroin [21, 32]. They are also used as adulterants in street heroin, cocaine, and methamphetamine, or as heroin substitutes sold to unaware users with a high risk of overdoses. Fentanyl and its derivatives have also been identified throughout Europe in counterfeit medicinal products, such as oxycodone, hydrocodone, and alpra-

zolam tablets, or as components of speedball mixtures together with cocaine or other stimulants. Synthetic opioids have high abuse potential and pose a severe risk of life-threatening poisoning, as they can cause severe respiratory depression leading to coma and death [33]. Due to their high potency, few grams are sufficient to make many thousands of doses for the drug market [34]. This makes them easier to import undetected into the Schengen Area, as small letters and packages can easily be disguised. In Italy, synthetic opioids were identified mostly in seizures, tramadol, fentanyl, isobutyrfentanyl (iBF) and 4-fluoro-isobutyrfentanyl (4F-iBF) being the most frequently reported. Tramadol was also involved in few acute intoxications. Three deaths associated with the consumption of two fentanyl derivatives (ocfentanil and furanylfentanyl) and of U-47700, another synthetic opioid, were reported during 2017-2018.

From June 2016 to June 2020, 49 NPS were identified for the first time in Italy in seizures and/or cases of acute intoxication and/or deaths reported by the Collaborative Centers network. These NPS belong mainly to the chemical class of synthetic cathinones (34.7%), synthetic cannabinoids (18.4%), arylcyclohexylamines (12.2%), and synthetic opioids (10.2%). Similarly, synthetic cathinones and synthetic cannabinoids account for the majority of the total number of NPS notified to the EU EWS for the first time in the considered period [25]. The larger number of synthetic cannabinoids identified for the first time at EU and national level reflects their use as “legal” replacements to cannabis, which is the mostly commonly used drug in Europe. The larger number of synthetic cathinones reported for the first time at EU and national level reflects their use as “legal” replacements for large markets in cocaine, amphetamines, MDMA, and other controlled stimulants.

When a NPS is identified for the first time in Italy, a document called “Reporting form” is issued by the SNAP under the supervision of the DPA, and then sent to the EMCDDA to quickly update the EU EWS network. The Reporting form includes information about the circumstances of the event (i.e., seizure, intoxication), chemical and analytical data, and any other relevant information. Analytical data facilitate NPS identification by laboratories across Europe, especially when a NPS is identified for the first time. Isobutyrfentanyl and 4F-furanylfentanyl and the 2F-QMPSB, a synthetic cannabinoid, were detected for the first time in the EU in Italy during 2019-2020.

Reporting by Member States allows the EMCDDA to constantly monitor NPS throughout Europe. The acquired informations allow to detect and assess any potential threats in a timely manner, and to improve any response measures that might be needed at a national or EU level.

Phase 2 – Risk assessment

The risk assessment concerns health and social risks embedded in NPS manufacture, trafficking, and use. Based on the information reported by the EU EWS and the national Collaborative Centers network, the three SNAP operating units generate a number of outputs to provide timely awareness to the national network.

The most relevant warnings are the “Alerts”, providing vital, time-sensitive information for a specific event or situation associated with a NPS that may pose a serious public health or social risk in Italy. Alerts are classified according to the seriousness of the event and its consequences on health (I, II, and III degrees). Grade I alerts refer to a phenomenon with a risk of social unease (worry, anxiety, conditions of social alarm). Grade II alerts are associated with a risk of minor damage to health (temporary non-lethal disorders) and spreading onto the illicit market. Grade III alerts involve a concrete risk of serious damage to health (disabling diseases, deaths).

From June 2016 to June 2020, the SNAP issued 52 alerts (14 grade I, 14 grade II, and 24 grade III alerts), the majority of which involved cases of NPS acute intoxications in Italy that were reported by the Collaborative Centers network. Other alerts concerned NPS that had been involved in severe public health and social risk at the European level, such as the use of NPS as adulterants (i.e. Cannabis adulterated with synthetic cannabinoids) or as fake medicines (i.e. benzodiazepines).

Almost 20 alerts involved fentanyl and derivatives. Fentanyl derivatives are a group of synthetic opioids with a long history of illicit use as substitutes for heroin and other controlled opioids [35]. From their first appearance in 2012 on the European drug market, 34 fentanyl derivatives were identified in Europe, and were involved in more than 250 deaths in Europe at the end of 2018, as reported by the EMCDDA [36].

The rapid growth in the number and identification of fentanyl derivatives in Europe is reflected at the Italian national level. Ocfentanil and furanylfentanyl were responsible for two deaths in 2017 and 2018. Moreover, it was the first time that these molecules were detected in Italy. Afterwards, carfentanil, butyrylfentanyl, tetrahydrofuranylfentanyl (THF-F), acetylfentanyl, and methoxyacetylfentanyl were identified for the first time in Italy; isobutyrylfentanyl and 4F-furanylfentanyl were identified for the first time in Europe in seizures by law enforcement on the national territory.

Phase 3 – Control measures

At the Italian national level, the reference text for the cultivation, production, trade and use of narcotics and other psychoactive substances in Italy is the “Testo unico delle leggi in materia di disciplina degli stupefacenti e sostanze psicotrope, prevenzione, cura e riabilitazione dei relativi stati di tossicodipendenza (Consolidation of the laws governing drugs and psychotropic substances, the prevention, treatment, and rehabilitation of drug addicts)”, referred as Presidential Decree 309/90. All narcotic drugs and psychoactive substances are listed in four Tables (I, II, III, and IV), indexing the substances

with strong addictive liability and potential for abuse; these Tables are amended whenever a substance should be introduced, reclassified, or removed. Updating the Tables involves a complex process of discussion and coordination between the Central Narcotics Office of the Ministry of Health, the ISS, and the Superior Health Council [37].

SNAP information on the NPS circulating in Europe and Italy allows prompt legislation. NPS inclusion in the Tables of the Presidential Decree 309/90 thus allows the police to combat trafficking and user exposure to potential health risks.

From June 2016 to June 2020, 139 NPS were included in Table I of the Presidential Decree 309/90. These substances are classified based on their chemical structure, opioids (25.2%), synthetic cannabinoids (19.4%), and phenethylamines (15.1%) being the most represented.

CONCLUSION

In the last years the operating national network on NPS has represented a point of integration and coordination between the various national and European actors involved in response activities to the spread of NPS. The future developments of these substances are difficult to predict, with possible growing health and social harms linked to the appearance of more potent molecules or new consumption patterns. To respond to such a dynamic and complex scenery, the coordination of local, national, and European efforts needs to be consolidated and the development of new tools for collecting, analysing and reporting on all aspects of the NPS phenomenon is highly recommendable.

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Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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