

New Psychoactive Substances: A Matter of Time

Flaminia Pantano^a, Silvia Graziano^b, Roberta Pacifici^b, Francesco Paolo Busardò^{c,#} and Simona Pichini^{b,#,*}

^aDepartment of Anatomical, Histological, Forensic and Orthopaedic Sciences, Sapienza University of Rome, Rome Italy; ^bNational Centre on Addiction and Doping, Istituto Superiore di Sanità, Rome, Italy; ^cSection of Legal Medicine, Università Politecnica delle Marche, Ancona, Italy

Abstract: In the last few years, a wide range of new psychoactive substances (NPS) have been produced and marketed to elude the controlled substance lists. These molecules enter the traditional illegal and web market with poor knowledge about their toxicity, mechanism of action, metabolism, abuse potential so that they are directly tested by the consumers. This perspective highlights the main issues connected with NPS: the celerity they enter and leave the market once included in the banning laws to be substituted by new legal analogues; the unavailability of analytical screening tests and certified standards to perform toxicological analyses; the time lag between NPS identification and inclusion in the controlled substances lists. Finally, the authors take a snapshot of the commitment of the Italian Early Warning System in highlighting the recent seizures of NPS as well as the distribution of NPS related intoxication and deaths as an example of what is happening in the European countries and internationally.

Keywords: NPS, analog, toxicity, early warning system, controlled substances, toxicological analysis.

1. INTRODUCTION

The term New Psychoactive Substances (NPS) refers to "substances of abuse, in a pure form or in a preparation, which are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention" as defined by the UNODC [1]. Differently from the "traditional" drugs of abuse (*e.g.* opiates, cocaine, cannabis, amphetamines), whose pharmacotoxicological aspects have been known for a long time thanks to a wide range of international studies at the time NPS are marketed, very poor information on their mechanism of action, abuse liability and toxicity is available [2, 3]. Therefore, what usually happens is that NPS pharmacokinetics, pharmacodynamics, toxicity and abuse potential are directly tested by the consumers and only reported in web fora. For the above-reported reasons, any new NPS that comes to the light can pose a serious public health issue, as it has been in the case of illicit fentanyl analogs [4]. In that particular situation, dangerous effects were initially underestimated due to unawareness of users about the consumed product (often sold in place of heroin), difficulties in analytically identifying unscheduled compounds (whose pure standards were not readily available) and in correctly investigating intoxications (simply classified as heroin related deaths) [5].

Generally speaking, NPS are synthesized in place of illegal chemical or structural analogs to elude national and international banning laws. The "permanence on the street and web markets and their commercial price mainly depend on "consumers satisfaction" in terms of the balance between number and length of positive subjective effects *vs* eventual side effects. Whereas these two latter terms can be reported in web fora, acute intoxications requiring hospitalization and fatalities are not immediately available and often NPS users are not aware of the most threatening consequences of NPS [6-8]. For instance, despite several intoxication cases and fatalities published in the international literature, the "commercially successful" synthetic cathinones are still widespread throughout the illegal market and are the first most consumed NPS as a satisfactory alternative to cocaine, ecstasy and amphetamines [9-11].

Concerning neuropharmacology of NPS, the majority of the studies have been performed *in vitro* and on animal models and only on the most representative and used molecules of the different NPS class. Therefore, the mechanisms of action of the newer compounds are presently only supposed and when their mechanisms of action are elucidated, so as the health impact on the population, studied compounds are substituted by newer ones entering into the illegal market.

In vitro and animal studies on principal synthetic cathinones, (*e.g.* mephedrone, 4-methylmethcathinone, 3,4-methylenedioxypyrovalerone) have shown that they display their action through the impairment of monoamine plasma membrane transporters for serotonin (5-hydroxytryptamine, 5-HT) dopamine (DA) and norepinephrine (NE), substantially increasing their concentration and acting as psychomotor stimulants [12, 13].

*Address correspondence to this author at the Istituto Superiore di Sanità, Rome, Italy Tel/Fax: +39-06-49906545, +39-0649902016; E-mails: simona.pichini@iss.it

#Both Authors equally contributed to the paper.

Whereas several studies have been conducted on classic phenethylamines (e.g. amphetamines, methylenedioxyderivatives), only few have focused on the novel ones (e.g. MMA, 2C-I, 2C-T-2, 2C-T-7, TMA-2, 5-IT and 4-MA) and they are mainly *in vitro*, on animals models or toxicity reports [14]. Updated literature highlights that new phenethylamines can have an extensive range of effects depending on the substituents linked to the aromatic ring, varying from entactogenic and psychostimulant action to hallucinogenic effects. Their action can be globally ascribed to the interference with monoamine reuptake carriers, but some of them show agonism with $\alpha 1$ -adrenergic receptor and action on the trace amine-associated receptor (TAAR) [15].

The existing literature concerning new psychoactive tryptamines shows they act as agonists at multiple receptors, 5HT_{2a-1a-2c}, serotonin receptors and several ion channels interfering as well on TAAR [6, 15]. They generally display hallucinogenic properties, rather than stimulant or entactogenic characteristics. However, the mechanism of action and the effects of this class of NPS are still fragmentary and mainly based on *in vitro* and animal studies and consumer's self-reported experiences.

The majority of the studies including new psychoactive piperazines have focused on 1-benzylpiperazine (BZP), and are principally based on animal studies and on toxicity and fatality reports [16]. These compounds usually act as stimulants through monoamine transporters interaction but in other cases, they can act as opioids, binding to specific opioids receptors [17].

Information is available on the neuropharmacology of synthetic cannabinoids (SCs), synthesized in the 80's to mimic the ligands of the endocannabinoid receptor system and study them [18]. A wide range of SCs have been manufactured, each of which expresses a different and frequently unknown binding affinity for cannabinoid receptors CB₁ and CB₂, and therefore, a greatly dissimilar potency. However, SCs seem to act as a direct agonist towards CB receptors whereas $\Delta 9$ -tetrahydrocannabinol (THC) behaves as a partial agonist. However, little information is available about their effects on other signalling pathways that may be responsible for some of the effects of these substances [18].

The class of new synthetic opioids includes fentanyl and its illicit analogs and non-fentanyl derived opioids [4,5,8]. These molecules display their action on opioids receptors with great difference in binding affinity and potency and only few compounds included in the class have been extensively studied. Arylcyclohexylamines, display their action through the interference with several central nervous system (CNS) receptors, mainly the inhibition of N-methyl-D-aspartate (NMDA) receptor. Despite published information about some constituents of this class such as Ketamine and Phencyclidine, other compounds are scantily reported in the literature [19].

The fact that an NPS can rapidly enter the market and just as fast, go out of it because of poor behavioral and subjective effects, or after frequent and important adverse reactions to the population, that can result the lack of detection in biological fluids of consumers and often the impossibility to correlate toxic events and deaths to a specific substance [20]. It is highly probable that the most dangerous NPS may be those that quickly go out of the market, because of serious side effects, even before being seized.

The prompt analytical identification of a newly introduced NPS is affected by the unavailability of rapid screening tests to detect it in emergency departments and by the absence of analytical procedures and of certified reference materials (internal standard) to perform the analysis [4, 21]. Sometimes, when an NPS is identified by the Early Warning System based in US and in Europe and a pure standard is produced and available to perform the analysis, the substance is already out from the trafficking. Moreover, since for many NPS, metabolites are unknown, the detection of NPS consumption may become impossible especially if the substance is characterized by rapid and complete metabolism or if there is a wide time interval between its consumption and analytical investigation. Consequently, it is sometimes possible that the first cases of intoxication and death by a certain NPS are not even detected.

When an NPS consumption is finally identified and eventual side effects are disclosed and reported, there is necessarily a time lag between its identification and risk assessment and its inclusion in the banning laws of controlled substances. Sometimes when the NPS is included in the prohibited substance list, the molecule has been already replaced by an analog.

2. A SNAPSHOT ON THE ITALIAN NATIONAL EARLY WARNING SYSTEM ON NPS

The appearance of synthetic drugs in Europe during the late 1980s and early 1990s, required the enforcement of the European Union (EU) Early Warning System, a specific network coordinated by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), located in Lisboa, Portugal in close cooperation with Europol [22]. The network was set up to rapidly detect NPS, assess eventual related-risks, and respond to public health and social hazards caused by the appearance of always new NPS on the drug market. It has to be said that in the global context, Europe is an important market for psychotropic drugs and precursors, supplied both from domestic production and trafficking from other world regions.

Within the EU Early Warning System, the network national partners give a particular focus to seizures and cases of severe poisoning and deaths, which may have a great impact on public health or social harm. In Italy, the National Early Warning System (NEWS) interfaces with European and international institutions of the EU Early Warning System concerning every news and alert on NPS.

The Italian illicit drug market is dominated by large organized crime structures with well-established international links and operating bases in principal drug production and trafficking regions, such as South America, South-East Asia and northern and

south-eastern Europe. Moreover, a large proportion of illicit drugs pass through Italy *en route* to other European Union countries [23].

The Consolidated Law, adopted by Presidential Decree No 309 on 9 October 1990, represents the legal structure for trade, treatment and prevention, and prohibition and punishment of illegal activities in the field of drugs and psychoactive substances in Italy. Depending on the relative health hazard, the drugs are distributed into four schedules (more dangerous drugs in Schedules I and III, less dangerous drugs in Schedules II and IV) [24].

The schedules contain the list of all the substances indicated in the international conventions and agreements and are promptly updated with a ministerial decree whenever there is a need to include a new substance or to change its position within the Tables or to provide for a possible deletion on the basis of the necessities of the conventions and agreements themselves or new scientific acquisitions.

If an illicit drug seizures and its use by the general population is considered, in Italy, cannabis products dominate, followed by cocaine (10.2 and 1.2% prevalence of use in the previous year by 15-64 years old population). NPS are located at the third place with 0.7% use prevalence during 2017 in general population [23]. Despite the apparent low prevalence of NPS in the Italian territory, several NPS have been promptly included into the Schedules of the Presidential Decree No 309 on 9 October 1990, even if some of the seized ones are still legal.

During the last three years (2016-2018) of the NEWS activity, seizures concerning the NPS have been very limited even if with a slight increase through years (Table 1).

Table 1. Trends of NPS seizure in Italy. Years 2016-2018.

NPS Group	2016	2017	2018
Arylcyclohexylamines	1	5	6
Arylalkylamines	1	0	0
Cannabinoids	0	11	1
Cathinones	8	9	10
Indolalkylamines	1	3	14
Opioids	0	1	2
Other	1	3	5
Phenethylamines	9	7	11
Piperazines	1	0	2
Plants	2	2	4
Total seizures	22	39	51

The main classes of seized NPS are represented by synthetic stimulants like phenethylamines and cathinones.

Concurrently, during 2016-2018, non-fatal-intoxications and/or deaths linked to the use of NPS involved mainly synthetic stimulants (Table 2).

It is worth noting that three fatalities in the last two years were caused by the consumption of new synthetic opioids (1 case of U 47,700 in 2017 and 2 cases in 2018 of carfentanil and furanylfentanil). Since it took time (more than one year in the three cases) to disclose the compound causing the death [25, 26], the reports of deaths linked to these molecules in Italy could therefore represent the tip of an iceberg, considering that the absence of specific pure standards to confirm the analytical investigations may not allow a rapid identification of non-fatal intoxications and/or deaths.

This is not just the case of Italy. As before reported, in the last three years in Europe, there has been a large increase in the availability of new synthetic opioids, especially fentanyl derivatives. While they appear to play a small role in the overall market, since they account for only around 2 % of the total number of seizures of new substances, they are one of the fastest-growing NPS group monitored by the EU Early Warning System, with a total of 38 different synthetic opioids reported, 28 of which are fentanyl analogs. Increasing evidence of harms related to fentanyl derivatives, including reports of deaths and non-

fatal intoxications have been reported by several member states [4, 5]. These substances can be particularly risky, with minute quantities capable of causing life-threatening poisoning and death from rapid and severe respiratory depression [4, 5].

Table 2. Trends of NPS related intoxications/deaths in Italy. Years 2016-2018.

NPS Group	2016	2017	2018
Arylcyclohexylamines	9	7	6
Arylalkylamines	0	0	0
Cannabinoids	0	0	0
Cathinones	5	4	8
Indolalkylamines	0	2	3
Opioids	1	3	2
Other	1	6	0
Phenethylamines	2	4	1
Piperazines	1	0	0
Plants	2	9	1
Total cases	21	35	21

It appears that most shipments of new fentanils coming into Europe originate from companies based in China, whereas the production in illicit laboratories in Europe has been reported occasionally. Since late 2015, the EMCDDA has conducted joint investigations with Europol on eight fentanils that have caused serious concern at European level and so far, two of them (acryloylfentanyl and furanylfentanyl) have been subject to control measures at EU level. For this reason, many member states have included fentanyl and its illegal analogs in the banning laws, and this has been also the case of Italy. Nevertheless, it should be considered that few grams of these molecules are often sufficient to make many thousands of doses for the drug market, and can be easily concealed in a small package. This can make it harder for customs and border forces to detect and intercept their trafficking.

CONCLUSION

During the last decade, NPS have supplemented with classic drugs of abuse generating a global health issue. The Italian example reflects the complexity and the uncertainty of the NPS situation and underlines the importance of continued investment in effective functioning of Early Warning Systems at both national and EU levels, as well as a more rapid risk assessment process at EU level in order to protect the health and security of the population.

The great difference between the classic drugs of abuse (cannabinoids, cocaine, amphetamine, opioids) that in any case overcome the market, and NPS is that presently the drug life (coming in and coming out from the markets) is so rapid that there is no time to focus on neuropharmacological aspects and side effects of these substances, no time to set up a proper analytical method to identify and quantify them in seized non-biological specimens and biological matrices of users and the inclusion in the banning law occurs late, when the new synthesized analog has already substituted the previous one.

In conclusion, the main issues of NPS are the fluidity and speed to enter and exit the market, their unknown and unpredictable effects on health, lack of prompt analytical detection and the rapidity to be replaced by other analogs to elude the law, in a word all that is around NPS is a matter of time.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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