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Detecting Novel Psychoactive Drugs around the World

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Abstract

Purpose of review. The worldwide spread of novel psychoactive substances (NPS) in the illicit drug market and their continuous increase in number and type, in relation to the purpose of bypassing the controlled substance legislation, represents an unceasing defy for forensic scientists, clinicians and enforcement authorities. We aim to provide information regarding the most urgent harms related to NPS consumption in different world regions and the current state of the art for NPS analysis.

Recent findings. Unfortunately, the identification of NPS in biological samples is controversial, especially when the examined samples are limited, or the drug is promptly and extensively metabolized. This causes a lack of information on their real diffusion in different parts of the world and in different groups of populations. New technologies and instrumental detection of NPS in alternative samples are offering comprehensive information about the NPS use.

Summary. The lack of detection and underreporting of NPS in biological samples makes it difficult to obtain complete qualitative and quantitative information about the NPS prevalence. The most innovative strategies that have been proposed in the last two years to assist NPS analysis and possibly facilitate the understanding of the NPS diffusion around the world are presented.

Keywords: NPS, synthetic opioids, hair analysis

1. In which the detection of NPS is introduced

Since the publication of the first articles describing Novel Psychoactive Drugs (NPS) existence, their identification and quantification in biological and non-biological matrices represents a cumbersome process for most laboratories performing drug testing [1]. The analytical challenge involves not only the large variety of NPSs' chemical structures, but also the rapidity with which single NPS emerge and change or disappears, and the variety of specimen that are submitted to the toxicological analysis.

Given the rapid evolution of the recreational drugs market in terms of number of new substances being identified every year [2], simple and selective mass spectrometry-based multianalyte methods are developed and validated around the world for the discrimination of NPS, their isomers and their principal metabolites. Several methods have been successfully applied to the most common biological matrices, including urine [3], blood [4], oral fluid [5], hair [6], and postmortem specimen [7]. Both the parent drugs and their metabolites, the latter essential to confirm active drug use, are routinely identified. The choice of the most appropriate specimen and related screening and confirmation analytical methods usually depends on the specific advantages and disadvantages [8*]. A mindful and well-judged approach becomes crucial every time the NPS analyses are applied in different emergency and forensic toxicology contexts, including seized products analysis, drug of abuse monitoring, fatal and non-fatal intoxication cases, and anti-doping controls [9,10]. In this scenario, the inter-laboratory comparison of the applied techniques and the corresponding results for NPS detection by means of proficiency testing, is encouraged [11].

As a matter of fact, most analytical procedures are generally based on the targeted detection of a limited and well-defined list of compounds to monitor, usually chosen based on national or international reports, or alerts from national warning systems. Most multi-component methods that enable the NPS analysis are based on low-resolution tandem mass spectrometry [12]. More recently, broad-spectrum HRMS methods which features high mass accuracy for untargeted screening analysis, have become of particular interest [13]. Besides the possible elucidation of the structures of unknown designer drugs [14,15], innovative data analysis and machine learning

techniques for results interpretation [16,17**] have been developed and can successfully be applied to NPS metabolite investigation [18].

The NPS use does not represent a local issue. The globalization of the NPS problem, often organized by transnational criminal organizations, is greatly facilitated by the ease of procurement via the web, where illicit substances can be anonymously purchased online and delivered virtually to any destination. In this review, the NPS detection in different world regions is explored.

2. In which the detection of NPS in North America is described

The NPS use of in North America appears to be dramatically widespread [19] and accompanied by an escalating crisis of synthetic drugs overdoses. However, relatively little NPS production is seemingly located in the U.S., while its distribution is focused on final processing, dilution/cutting and packaging of substances imported from China or other Asian or European countries [20]. The overdose epidemic is currently being driven by synthetic opioids (NSO), and predominantly by illicitly manufactured fentanyl and its chemical analogs. More recently, rising non-fentanyl synthetic opioids [21], such as 2-benzylbenzimidazoles (also known as nitazenes; e.g. isotonitazene), brorphine [22,23], U-series analogues (e.g., U-47700), and NSO structurally related to methadone, have taken the lead in the number of non-fentanyl-related new analogues [24].

Many further NPS have been reported in north American territory. According to the Drug Enforcement Administration's 2022 Annual Emerging Threat Report [25], the MDMB-4en-PINACA is the most reported synthetic cannabinoid and N,N-dimethylpentylone the most reported cathinone in the U.S.. The most prevalent NPS benzodiazepine in 2022 was clonazolam and fentanyl was the most reported opioid. Quite alarmingly, it was also reported that - in 2022 - approximately 23% of seized fentanyl powder and 7% of seized fentanyl pills contained xylazine [26].

Further comprehensive data are produced from the Center for Forensic Science Research and Education's (CFSRE's) NPS Discovery. In 2023, NPS Discovery reported the detection of 17 NPS for the first time. Opioids, stimulants, and cannabinoids represent the largest subclasses observed [27]. Noteworthy, a reduction in fentanyl-analogues positivity together with a gradual shift toward a new generation of non-fentanyl-related synthetic opioids was observed [28]. Mixtures consisting of a wide variety of other drugs have also been reported [29]. The recent detection of nitazenes' analogues in biological samples represents noticeable evidence of this emerging threat. Metonitazene was quantitatively confirmed by LC-MS/MS in 20 authentic forensic post-mortem

cases with an average concentration in blood at 6.3 ± 7.5 ng/ml (median: 3.8 ng/ml, range: 0.5–33 ng/ml, n = 18) and in urine at 15 ± 13 ng/ml (median: 11 ng/ml, range: 0.6–46 ng/ml, n = 14). Metonitazene was the unique opioid identified in only 30% of these cases, but its occurrence in combination with fentanyl (55%), NPS benzodiazepines, opioids, and hallucinogens (45%) was predominantly found [30].

While validated and proactive workflow for the targeted detection and quantification of brorphine [31] and nitazenes analogs in biological samples are certainly needed [32,33], such a complex and alarming drug scenario urged the scientific community to address considerable efforts to improve the NPS detection, possibly bypassing conventional screening techniques and targeted analysis relying on known-substances libraries.

A promising example for general nitazenes detection is given by the potential of new bioassays, used as first-line screening tools for the universal opioid NPS detection in biological samples [34**]. In a recent publication, the presence of opioid activity in two authentic samples (serum and urine) was confirmed after their disclosing by an activity-based screening assay. A concomitant quantitative analysis of N-piperidinyl-etonitazene via LC-HRMS revealed concentrations of 1.21 ng/mL in serum and 0.51 ng/mL in urine. In light of the opioids diffusion in the U.S. and their online availability, it is most likely that further hazardous compounds are present in the northern American territory [35].

A simple, cheap, and effective mean for low-concentration nitazenes' testing is represented by a blood microsampling technique known as Dried Blood Spots (DBS). Very recently, the UHPLC-MS/MS detection of a large panel of novel opioids after DBS sampling was presented [36*]. The DBS procedure appears to be advantageous, especially for large-scale epidemiological studies, since the sample collection is significantly less invasive than by intravenous needle draw. Secondly, the sample collection itself, and its transportation and conservation requirements are particularly simple.

A final opportunity to explore the diffusion of a wide NPS range in selected populations is offered by hair analysis. A total of 60 samples from an ongoing street surveillance study conducted throughout various U.S. cities by the National Drug Early Warning System was collected in 2022. Most of the participants reported either past 12-month use of heroin and/or fentanyl or at least one NPS, while a random participants sample did not report any heroin, fentanyl, or NPS use. The results suggested that fentanyl is the most prevalent used drug while the less common analogs tend to be co-used with other drugs and are not consumed in isolation [37].

3. In which the detection of NPS in Europe is described

Legislative controls in Europe and non-EU source countries apparently contributed to a reduction in the number of new derivatives entrance, yet in 2021, a record 8.5 tons NPS was seized by EU Member States [2]. The numerous seizures suggest that these substances circulate throughout Europe and are extensively used therein. Indeed, several new molecules belonging to different classes are recurrently detected in ante-mortem samples [38,39], post-mortem cases [40–44] and non-biological specimen [45], such as blotter [46] and soaked letters smuggled into the prisons [47,48]. The number of people who turn to NPS to temporarily escape from personal or social problems, such as unemployment, homelessness and/ or incarceration, is increasing. A recent study found that synthetic cannabinoids were linked to nearly half of male non-natural deaths in England and Wales prisons [49].

Synthetic cathinones [50] and new synthetic opioids [51,52] are relatively well-established in some European drug markets. They are sold as replacements for stimulants such as amphetamine or opioids such as heroin, respectively. While synthetic cannabinoids (SCs) are apparently the most widespread NPS class in Europe, hair testing proved to offer a confirmation together with an unique perspective in the investigation of NPS consumption [6]. An interesting investigation for SCs use on 5097 hair samples was conducted in Germany in the context of driving re-licensing testing [53*]. With a positivity rate of 3.6%, SCs appear not to be “niche drugs” anymore. Furthermore, there is a growing concern that traditional consumers cannabis may be at risk of inadvertent exposure to SCs [54–57].

Analytical methods for the detection of both parent SCs and their metabolites in biological samples are available [58–60]. LC-MS/MS assays are the most widely used approaches for the selective identification of SCs, although the lack of standard references for the new SCs and the need for methods’ revalidation due to their continuous emergence represent limiting factors for the plain adoption of this techniques. Again, a potential solution is offered by high-resolution mass spectrometry screening, which allows for non-targeted detection and retrospective data interrogation.

The most notable recent innovation in SCs testing is aimed to develop a generic approach to detect SCs in portable settings. As aforementioned, the majority of SCs enter the jail after being adsorbed

onto physical matrices such as paper, fabric, or herb materials. In order to detect the presence of a substance possibly belonging to the SCs class, a low-cost hand-held, fluorescence-based device with essentially immediate detection was developed [61**]. Enhanced chemometric and machine learning approaches will likely assist in the future the discrimination of complex drug/matrix signals.

4. In which the detection of NPS in Asia and Oceania is described

The prevalence of synthetic drugs, particularly NPS, continues to pose significant harm risks for drug users in East and Southeast Asia. The number of individual NPS annually identified showed a downward trend in recent years, partly due to the implementation of legal controls and measures. However, scattered new substances continue to emerge [62], among which synthetic cannabinoids account for the largest proportion. Again, hair analysis has been extensively applied to investigate the prevalence of SCs in Asian countries. Multianalyte methods were developed and applied in China [63,64**], showing that MDMB-4en-PINACA had the highest positive detection rate in the tested population.

Following the SCs class scheduling by methods addressed to identify the common features of their chemical structures, several substances designed to circumvent legal controls emerged (July 2021) in China [65], including a new “OXIZID” class of synthetic cannabinoids. This trend continued into 2022, with five new synthetic cannabinoids identified in the country, including BZO-4en-POXIZID [62]. Remarkably, hair analysis enabled to identify five exposure cases to BZO-4en-POXIZID which occurred in 2021 in the United States [66], suggesting that these SCs may have been exported from Asia many months prior to the Chinese ban.

Australia seems to be facing a public health emergency related to benzodiazepine-type NPS into illicit drug markets since the 2000s, either as stand-alone products or as adulterants in counterfeited tablets [67]. Benzodiazepine-type NPS consumption is possibly lured by their relative low cost and availability without a prescription. Consequently, benzodiazepine-type NPSs have been increasingly identified in biological specimen, particularly in polydrug overdoses [68]. From a total of 1112 cases recorded between September 2020 and August 2022, the detection of at least one benzodiazepine-type NPS was analytically confirmed in 183 overdose cases (16.5 %), with clonazolam being the most frequently detected benzodiazepine-type NPS [68].

5. Conclusions

The evidence reported in this review indicate that toxicological screening and confirmation methods need to be continuously updated to include new substances emerging on the drug market. Furthermore, alerts notified by coordinated early warning networks offer close to real-time detection of unexpected substances and provide rapid, evidence-based drug market intelligence to inform preventive and responsive action to drug-related harm [69,70]. Indeed, results from non-biological analysis may represent a collateral source of information on the possible toxic agent and provide reference material the laboratory so as to help the discovery of new emerging substances.
The end-users who purchase online NPS could never be guaranteed that the material actually supplied will correspond to the one ordered; they are constantly at risk of receiving an unknown drug instead of that they previously used (or were addicted to), enhancing the chance of overdose. Also, the purity of the supplied NPS is always unknown, creating health risks due to unexpected effects and potencies which in turn may lead to intoxication and fatal overdoses.
Opioids, synthetic cathinones, phenethylamines/amphetamines and synthetic cannabinoids are the main NPS classes found in the biological samples, and polydrug use was reported in most studies, which exposes NPS users to a higher overdose risk due to potential drug interactions. Some drugs, particularly among synthetic cannabinoids and opioids, can be fatal at low doses, which makes their detection in fatal overdoses and the consequent toxicological evaluation particularly challenging. The lack of detection and underreporting of NPS in biological samples, together with the scarcity of toxicological studies addressed to establish the risks caused by NPS consumption, make it difficult to understand the real impact of NPS in intoxication cases.
In this scenario, worldwide efforts are daily put in place by toxicological laboratories. Technological developments and scientific research, combined with a prompt alert networks, may offer the most effective solution to face the public health threaten of NPS diffusion.

Key points

- NPS is global threaten presenting diversified features across the world
- Various technologies are being used to detect the presence of NPS in drug samples

- Relentless research and development of new technologies can offer effective solutions to face the public health threaten of NPS diffusion.

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