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Biosampling strategies for emerging drugs of abuse: towards the future of toxicological and forensic analysis

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ABSTRACT

The term "new psychoactive substances" refers to emerging drugs of abuse whose chemical structure and psychoactive effects are similar to other already known compounds, often providing a "legal" alternative to internationally regulated drugs and mostly available *via* on-line retail sites. There are several categories of new psychoactive substances, such as synthetic cannabinoids, cathinone analogues, phenethylamines, tryptamines, and the need to identify and quantify an unprecedented and growing number of new compounds represents a unique challenge for toxicological and forensic analysis.

The purpose of this review is to highlight biosampling, sample preparation and analysis of the most important classes of emerging drugs of abuse in biological matrices, focusing on alternatives to classical blood and urine "in tube" approach, still representing the standard routine for bioanalysis, despite inherent flaws regarding handling, stability and process feasibility.

Chromatographic techniques coupled to mass spectrometry are usually exploited to identify and quantify new psychoactive substances; due to their high sensitivity and selectivity, it is possible to determine low concentrations not only in plasma and urine, but also in alternative matrices like dried blood spots, oral fluid, hair, other body fluids and tissues. Current literature on analytical methodologies applied to these samples is still limited and a more thorough validation is often required, including a comparison among the results obtained from conventional approaches and from innovative strategies, in order to determine their actual suitability.

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1. Introduction

New psychoactive substances (NPS) have been known in the market by terms such as "designer drugs", "legal highs", "herbal highs", "bath salts", "research chemicals" and "laboratory reagents". To promote clear terminology on such issue, United Nations Office on Drugs and Crime (UNODC) only refer to them as "new psychoactive substances (NPS)" which are defined as "substances of abuse, either in a pure form or a preparation, that are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat" [1–3]. The term "new" does not necessarily refer to new entities (several NPS were first synthesized 40 years ago), but to substances that have recently emerged on the illicit market and which have not been scheduled under the above Conventions. Due to a significant growth in the manufacture, sale and use of these products, it is necessary for forensic and toxicological purposes to have selective, sensitive and high throughput analytical methods to monitor NPS in marketed products and in biological matrices.

Over the past decades, bioanalysis has gone through extensive changes led by technological advancement; because of the development of highly sensitive techniques, the use of alternative matrices in the field of analytical toxicology has increased significantly. While blood and urine are still the most common exploited matrices, alternative ones such as dried blood spots, oral fluid and hair have gained considerable importance that should be carefully taken into account. These matrices are of particular interest as the time window of drug detection, and thus its interpretation, differs from traditional matrices. In addition, the collection is less invasive and the possibility of adulteration is dramatically reduced. The use of dried blood spot technique by finger puncture collected on filter paper is a consolidated practice in screening tests for neonatal metabolic diseases since long time [4] and represents a promising approach for analytical-toxicological purposes, as haematic matrices are the optimal strategies for drug of abuse analysis. Only recently, a few papers started to appear in the scientific literature

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regarding the use of dried blood spots for the determination of a variety of classical illicit substances [5,6]. Oral fluid can be useful to detect recent drug intake [7], while keratinous matrices such as hair [8,9] and nails [10] are used to provide information on long term drug exposure. While biological fluids and tissues like meconium [11], cerebrospinal fluid [12] and vitreous humor [13] are still mainly used for research purposes or in specific cases, DBS, oral fluid and hair have become key matrices for certain applications. Oral fluid has gained popularity in the field of workplace drug testing [14] and within driving under the influence of drugs (DUID) programs, owing to its ease of collection and narrow detection time window [15]. Hair is applied on a routine basis for establishing a timeline of consumption or to detect historical drug use [16]. This is of interest in the field of driving license re-granting [17] or drug-facilitated assault cases [18].

This review sums up and comments new trends regarding sampling and pretreatment procedures for the analysis of emerging drugs of abuse in different matrices, alternative to classical "in tube" haematic and urinary approaches. The review discusses advantages and limitations regarding the overall workflow feasibility, thorough validation and data reliability whenever the obtained results were compared to those from routine protocols. It could be helpful for many analytical and clinical toxicologists in their practice for both ante- and post-mortem investigation and for development of new methods. The presented topics can also be interesting for professionals dealing with roadside, workplace and sports drug testing settings, where the availability of large biological sample volumes may be limited; when there is a risk of sample tampering; when there is the need for complementary evaluations (such as past drug consumption habits); or where simple, high throughput sample processing and analysis are needed.

In this perspective, the current challenges in method development, with a look at the future of pharmaco-toxicological and forensic analysis will be discussed herein.

2. Emerging drugs of abuse: an overview

Over the past few years there has been an unprecedented increase in the variety and availability of NPS in Europe and worldwide. In agreement with this trend, during 2014 a total of 101 new substances were reported for the first time [19]. This brings the total number of compounds being monitored by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) to more than 450 (almost twice the number of substances controlled under the United Nations international drug control conventions), with almost half of them being detected for the first time in these last few years [20].

Between 2008 and 2013 a seven-fold increase in the number of seizures has been recorded for example in Europe, where synthetic cannabinoids were sold as alternative to cannabis and accounted for the majority, while synthetic cathinones were the second largest group considered as a replacement for amphetaminic stimulants.

International NPS diffusion has become a severe problem of the highest concern, also because these psychoactive molecules, although on the basis of a still limited literature, might induce frequent conditions of tolerance and dependence [21,22]. This international concern led to the setting up of the "Early-Warning System" (EWS) in the European Union [19], whose main task is to spread information on NPS to the countries included in the network, in particular considering those compounds that can cause social and public health problems. In this perspective, NPS use and diffusion among the population may affect traditional approaches adopted by analytical and forensic toxicology to monitor illicit consumption.

The overview on NPS presented throughout this review is based on the identification of four main groups of substances available on the illicit market, i.e. synthetic cannabinoids, synthetic cathinones analogues, phenethylamines, tryptamines and a group of miscellaneous compounds related to ketamine, GHB and fentanyl.

Given the virtually infinite chances in altering chemical structures, the list of substances mentioned in each of the cited groups is not exhaustive and just suggests guidance on the most common reported compounds. This review does not include those substances that are subjected to international controls under the 1961 Convention on Narcotic Drugs [2] or under the 1971 Convention [3]; benzodiazepines, for instance, or any other prescription prone to abuse, such as opioids, have not been considered in this review.

2.1. Synthetic cannabinoids

One of the largest groups of NPS-based products is represented by smoking mixtures containing synthetic cannabinoids (SC), intended as an alternative to natural cannabis. They became popular in Europe by the "Spice" brand in the mid-2000s, sold as herbal mixtures, initially under the guise of incense or home fragrances and then hundreds of different products have been advertised and sold, usually with the warning "not for human consumption". However, they must be actually smoked in order to produce strong THC-like effects. These illicit compounds have also been responsible for a high number of serious harms in recent years, such as intoxications requiring emergency treatment [23–25].

SC have been originally designed with therapeutic intents to act on cannabinoid receptors (CB1 and CB2) [26]. Since then, a solid investigation was implemented, achieving hundreds of new molecules characterised by binding affinities for CB receptors.

By the end of 2011, six major groups of SC receptor agonists have been set up: naphthoylindoles, naphthylmethylindoles, naphthoylpyrroles, napthylmethylindenes and phenylacetylindoles; Fig. 1 shows principal representatives of SC structural classes.

A comprehensive overview on SC pharmacology is not yet available, in terms of pharmacokinetics, such as the absorption, distribution, metabolism and elimination and also regarding pharmacodynamics, including psychomotor and physical effects. General pharmacokinetics and toxicology data are only reported for a few deeply studied compounds and in those cases of SC intoxication after consumption [27–29].

From an analytical point of view, the knowledge about active and also inactive metabolites is fundamental to recognise the related parent compounds taken by the abuser. It was found that SC are rapidly metabolised [30,31] and several other metabolism studies are in progress, based both on *in vitro* experiments in human or rat liver microsomes to mimic the first phase metabolism [32–34] and on *in vivo* researches by urinary screening of subjects after SC smoking [35,36].

2.2. Cathinone analogues

Cathinone, the principal active ingredient in the leaves of the khat plant (*Catha edulis*), can be considered as the prototype from which a wide range of synthetic cathinones have been developed. Cathinone analogues (CA) appeared on the illicit drug market in mid-2000s: in 2005 methylone, MDMA analogue, was the first synthetic cathinone reported to EMCDDA. In 2007, some reports about 4-methylmethcathinone (mephedrone) use emerged, first in Israel and then in other countries and regions, including Australia, Scandinavia, Ireland and the United Kingdom [37].

Cathinone and its derivatives are closely related to the phenethylamine family; in particular cathinone, mephedrone and methylone are structurally related to amphetamine, metham-

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