Volume 3, Issue 5, 2025

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

DETECTION OF EMERGING SYNTHETIC DRUGS: A FORENSIC TOXICOLOGICAL REVIEW

Burooj Fatima[*1], Syed Ahad Mustafa Bukhari[2], Yasir Ali Lakho[3], Faraz Jatt[4], Habiba Fatima Syed[5], Amna Latif[6], Syed Shahnoor Shah[7], Muhammad Asadullah[8]

*[*1,3,4,5,7]Institute of Forensic Medicine and Toxicology, Liaquat University of Medical and Health Sciences, Jamshoro, Pakistan*

[2,8]Institute of Biological Sciences, Khwaja Fareed University of Engineering & Information Technology, Rahim Yar Khan, Pakistan

[6]Department of Forensic Science, Institute of Molecular Biology and Biotechnology, The University of Lahore

[*1]buroojfatima7@gmail.com

DOI: https://doi.org/10.5281/zenodo.15826307

Keywords
Synthetic drugs, forensic toxicology, NPS, designer drugs, drug screening, analytical methods

Article History
Received on 01 May 2025
Accepted on 01 June 2025
Published on 07 July 2025

Corresponding Author: *
Burooj Fatima

Abstract

The worldwide increase in the misuse of new synthetic psychoactive drugs has created unsolvable problems for forensic toxicologists, healthcare workers, and law enforcement. Emerging synthetic drugs, or new psychoactive substances (NPS) can include synthetic cannabinoids, cathinones, opioids, or designer benzodiazepines and are difficult to characterize due to their rapid development, chemical diversity, and potent pharmacological effects. There have been various reviews assessing NPS with respect to their classification and pharmacokinetics, detection methods, and analytical issues. They claim that the importance of toxicovigilance and early warning systems is important in detecting and managing the effects of new synthetic drugs, as well as the need for However, to improve forensic detection and control methods, multidisciplinary approaches must be adopted and implemented, especially in Pakistan. The evolution of drugs continues, and they need to be managed collectively, and at a minimum consistently, around the globe. Just as if there is a need to identify opportunities to fill these gaps in most aspects of research, legal control methods, or laboratory capacity, I trust that the piece will contribute to the expanding body of knowledge around how we may most effectively manage their forensic toxicology.

INTRODUCTION

Over the last twenty years, there has been an alarming uptick in the manufacture, distribution and consumption of synthetic drugs, commonly called novel psychoactive substances (NPS). These chemically made drugs are designed to create the same pharmacological effects associated with selective illicit drugs historically used by humans such as cannabis, cocaine, heroin, or benzodiazepines while avoiding existing drug control legislation [1]. Synthetic drugs remain undetectable to established drug screening methods, such as immunoassay and chromatography, because of new and novel structures and ongoing transformations. This presents an array of challenges for healthcare providers, forensic toxicologists, and

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

regulatory agencies. Additionally, the ability to purchase additional online vendors, the marketing tactic of "legal highs", and the lack of public awareness has hardly assuaged the escalating public health concern [2].

Synthetic drugs are generally classified by the synthesis and intended pharmacological effect as synthetic cannabinoids, synthetic cathinones, designer opioids, phenethylamines, tryptamines, and designer benzodiazepines. Synthetic drugs tend to be more potent and toxic than established corresponding illicit drugs, which can all lead to increased rates of acute poisoning, long-term neurological dysfunction, and potential morbidity and mortality. Due to unpredictable pharmacokinetics and poorly understood metabolic pathways, clinical management and postmortem toxicological investigation and interpretation can be difficult [3]. In addition, the extent of public misuse of synthetic drugs in youth and urban populations has implications for drug-impairment behavior concerns and violence drugs. Ultimately, the effective burden on emergency medical services is not an ordinary consideration when assessing the increased use of these synthetic drugs [4].

This paper reviews the forensic toxicology considerations of new synthetic drugs and will address classification, analytical methods, and detection concerns in biological specimens. We will also examine the context of toxicovigilance and worldwide databases to help combat the changing landscape of NPS. We will primarily focus on the context of Pakistan where gaps in legislation, forensic ability, and underreporting of synthetic drug use leave limitations to circumventing the upsurge of synthetic drugs. Essentially, by reviewing and collating contemporary knowledge, this paper intends to provide useful contributions in establishing useful forensic methods and regulations for the detection and control of synthetic drugs.

2. Categories of Emerging Synthetic Drugs

2.1. Synthetic Cannabinoids

Synthetic cannabinoids are designer drugs intended to bind with cannabinoid receptors in the brain, producing drug effects associated with delta-9-tetrahydrocannabinol (THC), the major psychoactive component of natural Cannabis. Synthetic cannabinoids differ from THC, however, by being more potent and having their physiological and psychological effects including paranoia, agitation, seizure, and acute psychosis. The ongoing production of these new synthetic cannabinoids sometimes there can be a large number of structural variants, making detection and regulatory control very difficult [5].

Synthetic cannabinoids are typically marketed as herbal blends with a variety of names associated with their brands, such as; "spice" or "K2," and "not for human consumption" to avoid regulation [6]. Forensic toxicologists have difficulty detecting synthetic cannabinoids because they are typically rapidly metabolized, and there are no standard immunoassays available for cannabinoids screening. Advanced analytical techniques like liquid chromatography with tandem mass spectrometry (LC-MS/MS) or high resolution mass spectrometry (HRMS) are needed identify the synthetic cannabinoid [7].

2.2 Synthetic Cathinones

Synthetic cathinones, referred to as "bath salts," are a type of drug that are structure-related to the naturally occurring stimulant, cathinone, present in the khat plant. Synthetic cathinones are chemical analogs developed to mimic the effects of other synthetic stimulants (examples: amphetamines, cocaine, MDMA) [1]. Synthetic cathinones work as a stimulant by increasing levels of dopamine, norepinephrine, and serotonin in the brain. The euphoric, alertness, and sociable high provide users with desired effects, but users can experience extreme agitation, paranoia/delusions, violent behavior, and cardiac toxicity as side effects [8].

Forensic detection of synthetic cathinones is incredibly complex due to the rapid metabolism of this substance as well as the continual production of new synthetic cathinones. There are stimulant effects that lead users to recreationally abuse synthetic cathinones and there are also potential complexities due to the variance in strength among products and the relatively short half-life of most stimulants [9]. The most reputable access methods for detecting cathinones in biological matrices, blood, urine, and hair, are gas chromatography–mass spectrometry (GC-MS) and liquid chromatography tandem mass spectrometry (LC-MS/MS). Further compounding the issue, forensic laboratories need to rely on up-to-

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

date reference libraries to identify newly developed derivatives that are synthetically produced that will likely not be found in the usual screening panels [10].

2.3 Novel Psychoactive Substances (NPS)

A novel psychoactive substance (NPS) is an ambiguous term that refers to new synthetic drugs that are not controlled by standard drug laws, but pose similar dangers. Depending on their properties, NPS can be stimulants, depressants, hallucinogens, and opioids, and can mislead users as legal, legitimate options for traditional illicit drug use. To counter drug trafficking, because of their molecular changes, rapid development, and distribution through online networks, NPS present a formidable consternation for forensic toxicologists and regulatory agencies [11].

The most troublesome aspect of the NPS problem is their ability to escape drug testing by using a different chemotype. In order to detect NPS, extremely sophisticated analytical techniques (e.g. high-resolution mass spectrometry (HRMS) and nuclear magnetic resonance (NMR) spectrometric methods) can be used for identification of molecular structure. In addition to developing the molecular structure for identification, NPS' unique pharmacokinetic and toxicological profiles will affect an accurate interpretation of all NPS types. Real-time recognition of drug trends and research into international surveillance systems, consensus databases, and databases, will be essential to find and control NPS [12].

2.4 Synthetic Opioids

A concerning category and class of drug are synthetic opioids (including fentanyl and its analogs and compounds) primarily because of their potency and risk of overdose. Without a doubt, many fentanyl analogs are known to be hundreds, or even thousands, of times as potent as morphine. Often these drugs are responsible for overdoses, since users are not aware they are using counterfeit medication, thereby limiting their ability to respond when they mix different supplies of drugs [13].

Forensic toxicology practitioners often use high-sensitivity techniques to detect synthetic opioids, because of therapeutic doses and short action of synthetic opioids, which can lead to rapid elimination from the body. Analytical method procedures and approaches include analysis using LC-MS/MS, HRMS, and high-sensitivity approaches to quantify and measure the concentration of synthetic opioids in blood, urine, or postmortem samples. Clinical and postmortem evident that synthetic opioids are an apparent significant occurring substance in forensic examinations, is creating pressure to be responsive in regards of toxicology panels for expansion and newly establishing reference standards for other drugs in the changing drug market [14].

2.5 Phenethylamines and Tryptamines

Phenethylamines and tryptamines are synthetic molecules related to the neurotransmitters dopamine and serotonin, and comprise a spectrum of psychoactive substances including the 2C- series (i.e., 2C-B) and dimethyltryptamine (DMT), often used for their hallucinogenic and stimulant properties. Selected substances of phenethylamines and tryptamines continue to grow in popularity especially within rave culture and social gatherings, and are often marketed as substitutes for ecstasy and LSD respectively. Nevertheless, they may have effects that are much more potent and less predictable than ecstasy or LSD [15].

From a forensic perspective, phenethylamines and tryptamines can represent do not represent analytical challenges due to their structural similarities to other hallucinogens, but because of their rapid metabolism? Since they are not often picked up by immunoassays and possibly only one or two phenethylamines and tryptamines are included, these compounds are usually analysed by chromatographic techniques paired with mass spectrometry. As new chemical analogs are produced, forensic labs must begin investigating phenethylamine and tryptamine even further, and must continue expanding their libraries and optimizing they must include methods made with sensitive, validated, and inexpensive tests to examine quantitatively low concentrations of compounds in both living and dead specimens [16].

2.6 Benzodiazepine Analogs ("Designer Benzos")

Designer benzodiazepines are synthetic analogs of medically approved benzodiazepines (e.g., diazepam, alprazolam) that have not been proven to be suitable for medical use but are increasingly encountered in forensic and clinical toxicology cases. Designer

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

benzodiazepines are often marketed on the internet as 'research chemicals' and are sometimes delivered as imitations of pharmaceutical medications. Its properties as a sedative-hypnotic drug makes it an attractive product for misuse and, when combined with other central nervous system depressants like opioid medications or alcohol, it can cause even greater concern [17].

One of the major hurdles in detecting designer benzodiazepines includes the lack of reference standards and limited information on the metabolic processes of designer benzodiazepines. Additionally, many designer benzodiazepines have not been included in the routine drug panels performed in clinical or forensic toxicologies requiring additional confirmatory data using targeted LC-MS/MS or HRMS to confirm their presence. If the trend of misuse continues around the world, particularly among those who seek legal alternatives to prescription medications, forensic toxicologists need to keep pace with newly emerging analogs and push for better regulation and awareness regarding their public health risks [18].

Category	Examples	Pharmacological Effect	Street Names / Forms
Synthetic Cannabinoids	JWH-018, AB-FUBINACA	Cannabinoid receptor agonists	Sold as herbal mixtures or "spice"
Synthetic Cathinones	Mephedrone, MDPV	Stimulant (like cocaine/MDMA)	Marketed as "bath salts"
Synthetic Opioids	Fentanyl, Carfentanil	Potent μ-opioid receptor agonists	Pills, powders, sometimes mixed with heroin
Phenethylamines	2C-B, NBOMe	Hallucinogenic	Tablets, blotters
Tryptamines	DMT, 5-MeO-DMT	Psychedelic	Powders, smoked, or ingested
Designer Benzodiazepines	Etizolam, Flubromazolam	Sedative-hypnotic, anxiolytic	Tablets or capsules
Other NPS	Methoxetamine, MXE	Dissociative, stimulant or depressant	Powder or capsule form

Table 1: Categories of Emerging Synthetic Drugs and Their Characteristics

3. Routes of Administration and Toxicokinetics

3.1 Routes of Administration

New synthetic drugs can be taken in different ways (for example by mouth, by smoking or vaporizing, by snorting, by injecting, under your tongue, through your skin), and depending on the route of administration, the pharmacodynamic effects of the drug on the user can vary in terms of onset time, duration of effect, and toxicity levels. Synthetic cannabinoids are usually smoked or vaporized; synthetic cathinones are mostly snorted or taken orally; designer benzodiazepines and synthetic opioids can be consumed in tablet, powder, or transdermal form which allows for rethinking the pharmacokinetics of synthetic drugs and makes them especially appealing to younger users and novice users [19].

Each route of administration is associated with varying types of risks. For example, inhalation and intravenous routes have much more rapid absorption and overwhelming effects with a presumably higher chance of overdose and toxicity. Oral administration may have a slower onset of effect but can have longer effects and possibly allow for delayed toxicity (especially with potent drugs such as fentanyl analogs) while transdermal and sublingual routes may skip hepatic first-pass metabolism and improve bioavailability. Understanding the route of administration is important in forensic exam casework to attempt to determine the timing of the intoxication and severity [20].

3.2 Toxicokinetics

The toxicokinetics (absorption, distribution, metabolism, and excretion) of synthetic drugs can be

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

highly different by drug class across indications. Many synthetic drugs are rapidly absorbed due to high lipophilicity and that absorption tends is often furthered when smoked, snorted, or injected. Once the drugs are in systemic circulation, they disperse throughout the body and become trapped in fat (or cross the blood-brain barrier to affect the central nervous system) [21].

This characteristic of distribution impacts the type of timeliness of, and collection methods for, forensic toxicology samples. Some drugs, like synthetic cannabinoids, have a large volume of distribution; therefore after a time, using blood or urine may fail to recover these drugs. Kinetics can be further influenced by unique user related factors like body composition, age, liver functioning and co- ingested agents. No single logic can be faithfully bought to the interpretation of pharmacokinetics; and consequently aligns toxicological findings (particularly with impaired driving charges or post-mortem) with contextual factors [7].

3.3 Metabolic Pathways and Biotransformation

Synthetic drugs often undergo complex metabolic processes, with the primary site of metabolism usually being the liver. Most of the drugs are metabolized by the cytochrome P450 (CYP450) system including CYP2D6, CYP3A4, and CYP2C19, where the key metabolic reactions include oxidation, hydroxylation, and dealkylation. The problem with new synthetic drugs and their wide diversity in structural forms means that researchers and toxicologists often do not know the metabolic pathway for many of these new compound classes. Understanding these pathways is also essential for toxicologists to identify metabolites in biological samples [22].

Some of the metabolites of synthetic drugs exhibit pharmacological activity or are actually parenter drugs that can be more toxic than the parent compounds. For example, some fentanyl analogs produce active metabolites that extend the respiratory depression. In some synthetic cannabinoids, many of the metabolites are psychoactive and contribute to the overall effects of the drug. Also, variations can occur within and between persons using the drugs, related to genetic variations in the expression of metabolic enzymes. These variations add difficulty to forensic interpretations. Therefore, it is essential to develop metabolite specific reference standards and methods to investigate them accurately [13].

3.4 Excretion and Detection Windows

Synthetic drugs, or their metabolites, are normally excreted through the renal system, but may also be present in sweat or feces, or as exhaled air. The speed of excretion is reliant on tems such as molecular size, polarity, speed of metabolism, and the hydration status of the individual. While usually the matrix of choice for drug screening is urine, there are limitations due to both excretion speed and detection time lapse, as the synthetic drugs may be excreted reasonably quickly and may not be detectable after a limited time post-use [23].

Excretion property detection windows vary widely across classes of synthetic drugs as well as across variants in classes. For example, the synthetic cathinones may produce a detection window of 24-72 hours in urine, while the synthetic cannabinoids may produce weeks or months depending on hair analysis. Detection windows are paramount in forensic toxicology and the interpretation of test results in a legal or clinical situation. If forensic toxicology needs to conclusively tell they must consider the sampling matrix and the time of testing for implications of the suspected drug and its known pharmacokinetic profile [24].

4. Analytical Techniques for Detection

4.1 Immunoassays

Immunoassays are used widely as a first-screening method in forensic toxicology, because of their prompt results, low-cost, and ease of automation. Immunoassays utilize antibodies that bind to either drug molecules or the metabolites of drug molecules. Common immunoassay formats include enzyme-linked immunosorbent assays (ELISA), radioimmunoassay (RIA), and fluorescence polarization immunoassay (FPIA). Although immunoassays are great for high-throughput assays, their lack of specificity and sensitivity for structural diversity of synthetic drugs, especially new psychoactive substances (NPS) are a concern [25].

One of the challenges with immunoassays is cross-reactivity, which results when antibodies bind to similar-structured compounds, leading to false positives and/or false negatives. The speed of

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

evolution of synthetic drugs means newly developed antibodies cannot keep pace, which means that most emerging substances cannot be detected via immunoassay kits; for this reason immunoassays cangenerate mass amounts of data, but they will eventually require confirmatory tests via advanced analytical methods for clear identification and quantification [26].

4.2 GC-MS (Gas Chromatography–Mass Spectrometry)

GC-MS is a confirmatory instrumentation method that is considered the gold-standard by many forensic toxicologists for the analysis of volatile and thermally stable compounds. It combines the separation capabilities of gas chromatography (GC) with the molecular identification capabilities of mass spectrometry (MS). GC-MS offers the toxicologist combined sensitivity and specificity that allows for the detection and quantification of a variety of synthetic drugs including such toxicants as cathinones and certain benzodiazepines. In particular, individual synthetic drugs that have structures that are closely related can also be differentiated based on their mass spectral fragmentation patterns [27].

GC-MS is limited with analyzing unstable or highly polar synthetic compounds that decompose upon heating, therefore derivitization (chemical modification to increase volatility or thermal stability) is sometimes necessary to analyze these toxicants in addition to creating additional complexity and time in the analysis. Moreover, GC-MS typically requires elaborate sample preparation that includes extraction and purification steps. Nevertheless, GC-MS remains a robust and suitable tool for forensic laboratories for the definitive identification of known synthetic drugs [28].

4.3 LC-MS/MS (Liquid Chromatography–Tandem Mass Spectrometry)

The method of choice for the detection of synthetic drugs in biological matrices with complex composition is LC-MS/MS primarily due to its sensitivity, selectivity, and versatility. Additionally, LC-MS/MS can analyze polar, non-volatile, and thermally-labile compounds without the constraints of derivatization, thus highlighting the opportunity to analyze synthetic cannabinoids and designer benzodiazepines. Mass spectrometry can run tandem mass spectrometry (MS/MS), which allows for multiple mass stages used to maximize specificity and reduce matrix components [29].

Another benefit for using LC-MS/MS is the plethora of quantitative analysis tools available at a larger range of concentration, which is advantageous for drugs in either a clinical or postmortem toxicology scenario. LC-MS/MS should also be able to analyze multiple classes of drugs in single run from a single sample with either targeted or non-targeted analysis. Limitations are only dependent on the availability of reference standards and methods as stipulated in protocols for the appropriate analytical chemistry, or because there are so many new synthetic drugs it involves constant revision of RMs, and continuous revision of new LC-MS/MS priorities, or standard LC-MS/MS databases and library so that the LC-MS/MS remains current in a diagnostic area, such as forensic toxicology [30].

4.4 High-Resolution Mass Spectrometry (HRMS)

High-resolution mass spectrometry (HRMS), utilizing Orbitrap, and time-of-flight (TOF) technologies, allows for accurate mass determination, making it a worthy alternative for forensic labs with regards to the identification of unknown or potential unknown novel drugs. HRMS provides identification based on molecular weight and isotope distributions and is thus especially well-suited to large non-targeted mass spectrometry approaches, which is essential when the compounds of interest are NPS specifically since there is no spectrum to rely on [31].

One of the most appealing aspects of HRMS is the potential for retrospective analysis. Once the data is collected, you can go back and reprocess the data to search for newly identified substances when most commonly you cannot get standards to identify the compound without redepositing samples and collecting more data. This capability is invaluable to forensic toxicology when timely identification of new or emerging compounds is necessary. Although it comes at a considerable cost and requires highly trained staff to perform, HRMS is a unique investment for a forensic practice to be able to realization change in the synthetic market [31].

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

4.5 Emerging Techniques

A few new analytical techniques are beginning to be utilized in forensic toxicology because they have the ability to qualitatively and quantitatively identify synthetic drugs more rapidly, sensitively, and in different contexts. The DART (Direct Analysis in Real Time) and DESI (Desorption Electrospray Ionization) ambient ionization methods can identify target drugs using little to no sample preparation time and can give near instant results. Certainly, their effects are felt acutely when screening unknown substances at crime scenes or at customs, where time is of the essence [32]. Portable instruments such as hand-held Raman and FTIR (Fourier-transform infrared) spectrometers, as well as portable mass spectrometers, are becoming more accessible and practical for on-scene forensic applications. Biosensors and microfluidic devices are under active development, and have the capacity to identify specific class types of drugs in real time. Though still in the validation stage, these new developments will fundamentally influence how synthetic drugs are screened and identified, while opening up new avenues for law enforcement and forensic professionals in the field, as well as in the laboratory [33].

5. Sample Types for Analysis

5.1 Blood and Plasma

Of all the biological materials available for forensic toxicology, blood and plasma provide some of the most useful information. Blood and plasma provide concrete evidence of the concentration of an active drug in gastric contents, which may be readily evident to the toxicologist, even if it may not be to the lay observer. Blood and plasma are also valuable, because they can demonstrate both the parent drug and the metabolites, providing the forensic toxicologist a means of ascertaining pharmacokinetic parameters, such as half-life, distribution, and bioavailability [34]. Whether blood, plasma, or both are favorable sample media will be influenced by the unique circumstances of each individual case; however, all biological materials have no special advantage or disadvantage, even considerations of tenability of use. Blood and plasma are useful in all toxicology screens that utilize a web-based platform, particularly with synthetic drugs. Blood is a required matrix in assessing acute intoxications, and is almost always expected in evaluation of driving under the influence (DUI) and drug-facilitated crimes [35].

Blood and plasma have a limited detection window comparatively to hair, possibly only hours/days after the date of ingestion, depending on the pharmacokinetics of the substance. This means that it is critical to perform blood sampling and blood is a required matrix for drug-facilitated crimes. Certain synthetic drugs, such as cathinones and synthetic opioids, have very short detection times; so blood sampling should occur at the earliest opportunity, and also blood, plasma, and urine samples should be stored appropriately after collection to ensure sample stability to minimize post-sampling and pre-analysis stability issues. In forensic science, both storage and treatment of samples, for everything from the analytical device/s being used to the pre-analytic sample, matters, as interferences, by-products, etc., can have substantial impacts on interpreting results ultimately [36].

5.2 Urine

Of all biological matrices, urine is the most common, because it is non-invasive to collect, it has a longer detection window, and perhaps more importantly, there are less drug metabolites in urine compared to other matrices. Urine is a retrospective measure of drug use in relation to its window of detection, whereas blood demonstrates current use. Urine is a viable matrix choice for drug screening for workplace testing, probation monitoring programs, and drug treatment centres. For synthetic drugs that are metabolised extensively, urine screening examines glucuronidated or hydroxylated metabolites (as opposed to the parent drug) [37].

There are limitations to using urine as a matrix as well. Urine cannot determine time of ingestion or current impairment status, as many drugs are detectable in urine days, weeks, or even months after cessation of effects. Urine is also more likely to be diluted and adulterated than other matrices to reduce the probability of detection. There are also new synthetic drugs to which the panel continuously updates for testing to ensure that novel drugs are ascertained in urine. However, urine will continue to be a practical and valuable matrix in forensic toxicology, as urine will allow for broad spectrum screening [38].

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

5.3 Hair

Hair testing provides a distinct advantage in forensic toxicology, which is having an extended, longer timeframe (> than days) for recording drug exposure. Depending on the length of the hair, it may present a record of exposure to drug use for potentially months. Drugs and their metabolites are incorporated into the hair shaft through the bloodstream at the time of hair formation. Once the drugs have been incorporated into the hair shaft, they are rendered stable, and for these reasons, hair is particularly useful for historical or retrospective examination of chronic or repeated drug consumption such as custody disputes, doping control, postmortem, or likely scenarios in which other biological specimens are not available or destroyed [39].

There are a number of variables in hair analysis that require consideration. The color of the hair, cosmetic treatments (bleach or dye), and the exposure to the environment can also affect the amount of drug incorporated/detectable and concentration measurements. Segmental analysis, cutting hair into sections representing observations of time, would support establishing a timeline for used drugs, this would require care in management, and practical use in laboratory analyses, ultimately it would require understanding, accurate calibration, and a fidelity to standard reporting practices. On the whole while hair testing might not be the best specimen used for a recent drug intake examination, it has a benefit for a low incidence of adulteration and degradation, and remains critically important for long on-going forensic toxicological investigations [39].

5.4 Oral Fluid

In forensic toxicology, oral fluid (saliva) is becoming increasingly accepted due to its non-invasive nature, ease of use, and strong relationship with many drugs concentration in the blood. Oral fluid does represent the free (unbound) fraction of a drug, which is active pharmacologically, enabling oral fluid to be a useful matrix for determining recent drug use and asking the question of impairment. Oral fluid testing has advantages in roadside screening or workplace screening in that it eliminates logistical concerns and reduces contaminated samples [40].

Oral fluid testing has some limitations including limited detection times of only a few hours for many of these drugs, especially synthetic stimulants and cannabinoids. Most people do not generate enough sample volume, rates of salivary pH and flow rate can also affect drug concentration. Also, some synthetic drugs may have poor transfer due to their particular physicochemical properties. However, oral fluid testing holds great promise as a specimen for rapid and on-site testing when timely testing and detection is required [41].

6. Role of Toxicovigilance and Early Warning Systems

Toxicovigilance is an important part of observing, defining, and evaluating associated harm and the public health risks posed by synthetic drugs. Toxicovigilance involves ongoing collection of data from poison centers, emergency departments and forensic laboratories in order to identify patterns, trends and emerging substances of misuse. Evidence based continuous observation will facilitate timely responses and policy framework development for the ongoing protection of the public health systems the healthcare and law enforcement communities need to respond to toxicology threats [42].

Early Warning Systems (EWS) managed by organizations such as the United Nations Office on Drugs and Crime (UNODC) and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) serve as global networks to disseminate information about new psychoactive substances (NPS) in real-time. The EWS helps countries work collaboratively and provides an opportunity for countries to describe trends and issues at the national and global level, sharing information in order to develop rapid communications to goverments, alerts to send those engaged in drug surveillance and to implement regulatory measures. In developing nations like Pakistan, addressing toxicovigilance in their national drug monitoring can help strengthen their forensic response capabilities [43].

Conclusion

The emergence of synthetic drugs is a rapidly developing and complicated matter for forensic toxicology. Synthetic drugs are rapidly evolving, often highly potent, and have the ability to circumvent existing regulation and it is causing forensic toxicology to find new analytical paths and respond in a

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

coordinated manner. The evolving nature of synthetic drugs is transforming healthcare systems, forensic laboratories, and law enforcement through its unpredictability and the lack of available data.

In Pakistan, as in other developing economies, there is an urgent need to improve forensic capacity, improve toxicological surveillance, and proactive policies. One of the goals must be interdisciplinary approaches between the health, legal, and forensic sectors. By bridging the gap between detection and fostering multi-faceted approaches, the forensic community can have a positive impact on public health and counteract some of the risks posed by these drugs.

References

1. 1. Ferrari, L.A., *Novel Psychoactive Substances (NPS): Update, Issues and Challenges.* Poison, 2024. **1**: p. 7-21.
2. 2. Lage, O.M., et al., *Current screening methodologies in drug discovery for selected human diseases.* Marine drugs, 2018. **16**(8): p. 279.
3. 3. Larchenko, A., et al., *Synthetic cathinones and cannabinoids are new psychoactive substances.* Современные технологии в медицине, 2017. **9**(1 (eng)): p. 185-196.
4. 4. Chang, C.Y., et al., *Burden of emergency conditions and emergency care usage: new estimates from 40 countries.* Emergency Medicine Journal, 2016. **33**(11): p. 794-800.
5. 5. Cohen, K. and A.M. Weinstein, *Synthetic and non-synthetic cannabinoid drugs and their adverse effects-a review from public health prospective.* Frontiers in public health, 2018. **6**: p. 162.
6. 6. Alves, V.L., et al., *The synthetic cannabinoids phenomenon: from structure to toxicological properties. A review.* Critical Reviews in Toxicology, 2020. **50**(5): p. 359-382.
7. 7. Castaneto, M.S., et al., *Synthetic cannabinoids pharmacokinetics and detection methods in biological matrices.* Drug metabolism reviews, 2015. **47**(2): p. 124-174.
8. 8. Kersten, B.P. and M.E. McLaughlin, *Toxicology and management of novel psychoactive drugs.* Journal of pharmacy practice, 2015. **28**(1): p. 50-65.
9. 9. Gonçalves, J.L., et al., *Synthetic cathinones: an evolving class of new psychoactive substances.* Critical reviews in toxicology, 2019. **49**(7): p. 549-566.
10. 10. Delaney, S.R., D.H. Tacker, and C.L. Snozek, *The North American opioid epidemic: opportunities and challenges for clinical laboratories.* Critical Reviews in Clinical Laboratory Sciences, 2022. **59**(5): p. 309-331.
11. 11. Madras, B.K., *The growing problem of new psychoactive substances (NPS)*, in *Neuropharmacology of New Psychoactive Substances (NPS) The Science Behind the Headlines*. 2016, Springer. p. 1-18.
12. 12. Pasin, D., et al., *Current applications of high-resolution mass spectrometry for the analysis of new psychoactive substances: a critical review.* Analytical and bioanalytical chemistry, 2017. **409**: p. 5821-5836.
13. 13. Armenian, P., et al., *Fentanyl, fentanyl analogs and novel synthetic opioids: a comprehensive review.* Neuropharmacology, 2018. **134**: p. 121-132.
14. 14. Concheiro, M., et al., *Postmortem toxicology of new synthetic opioids.* Frontiers in pharmacology, 2018. **9**: p. 1210.
15. 15. Varì, M.R., et al., *New psychoactive substances–synthetic stimulants.* Wiley Interdisciplinary Reviews: Forensic Science, 2019. **1**(2): p. e1197.
16. 16. Graziano, S., et al., *Screening methods for rapid determination of new psychoactive substances (NPS) in conventional and non-conventional biological matrices.* Journal of pharmaceutical and biomedical analysis, 2019. **163**: p. 170-179.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

17. 17. Jones, J.L. and R. Malcolm, *Neurobiology and Treatment of Sedative-, Hypnotic-, and Anxiolytic-Related Disorders*. The American Psychiatric Association Publishing Textbook of Substance Use Disorder Treatment. Washington, DC, 2021. **295**.
18. 18. Moustafa, R.E., et al., *Designer benzodiazepines versus prescription benzodiazepines: can structural relation predict the next step?* Critical Reviews in Toxicology, 2021. **51**(3): p. 249-263.
19. 19. Weinstein, A.M., et al., *Synthetic cathinone and cannabinoid designer drugs pose a major risk for public health.* Frontiers in psychiatry, 2017. **8**: p. 156.
20. 20. Bakand, S. and A. Hayes, *Toxicological considerations, toxicity assessment, and risk management of inhaled nanoparticles.* International journal of molecular sciences, 2016. **17**(6): p. 929.
21. 21. Bertol, E. and D. Favretto, *Pharmacokinetics: Drug Absorption, Distribution, and Elimination*, in *Karch's Drug Abuse Handbook*. 2022, CRC Press. p. 133-178.
22. 22. Zhao, M., et al., *Cytochrome P450 enzymes and drug metabolism in humans.* International journal of molecular sciences, 2021. **22**(23): p. 12808.
23. 23. Coleman, M.D., *Human drug metabolism*. 2020: John Wiley & Sons.
24. 24. Alvarez, J.-C., N. Fabresse, and I.A. Larabi, *Prevalence and surveillance of synthetic cathinones use by hair analysis: an update review.* Current Pharmaceutical Design, 2017. **23**(36): p. 5487-5495.
25. 25. Ahsan, H., *Monoplex and multiplex immunoassays: approval, advancements, and alternatives.* Comparative clinical pathology, 2022. **31**(2): p. 333-345.
26. 26. Stevens, K.G. and T.L. Pukala, *Conjugating immunoassays to mass spectrometry: Solutions to contemporary challenges in clinical diagnostics.* TrAC Trends in Analytical Chemistry, 2020. **132**: p. 116064.
27. 27. Kabir, A. and K.G. Furton, *Applications of gas chromatography in forensic science*, in *Gas Chromatography*. 2021, Elsevier. p. 745-791.
28. 28. Valdez, C.A., et al., *Analysis of chemical warfare agents by gas chromatography-mass spectrometry: methods for their direct detection and derivatization approaches for the analysis of their degradation products.* Reviews in Analytical Chemistry, 2018. **37**(1): p. 20170007.
29. 29. Zhang, Y.-X., et al., *Benzodiazepines in complex biological matrices: Recent updates on pretreatment and detection methods.* Journal of Pharmaceutical Analysis, 2023. **13**(5): p. 442-462.
30. 30. Peris-Vicente, J., J. Esteve-Romero, and S. Carda-Broch, *Validation of analytical methods based on chromatographic techniques: An overview.* Analytical separation science, 2015: p. 1757-1808.
31. 31. Brown, H.M., et al., *The current role of mass spectrometry in forensics and future prospects.* Analytical Methods, 2020. **12**(32): p. 3974-3997.
32. 32. Li, L., et al., *Comprehensive comparison of ambient mass spectrometry with desorption electrospray ionization and direct analysis in real time for direct sample analysis.* Talanta, 2019. **203**: p. 140-146.
33. 33. Seelenbinder, J.A. and C.S. Robb, *Applications of Portable and Handheld Infrared Spectroscopy.* Portable Spectroscopy and Spectrometry, 2021: p. 227-247.
34. 34. Subramanian, M., *Toxicology: Principles and Methods*. 2019: MJP Publisher.
35. 35. Kunsman, G.W. and R.L. Hartman, *Human performance toxicology*, in *Principles of forensic toxicology*. 2020, Springer. p. 15-33.
36. 36. Oliver, C.F., et al., *Synthetic cathinone adulteration of illegal drugs.* Psychopharmacology, 2019. **236**: p. 869-879.
37. 37. Jaffe, A., et al., *Review and recommendations for drug testing in substance use treatment contexts.* J Reward Defic Syndr Addict Sci, 2016. **2**(1): p. 28-45.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

38. 38. Huppertz, B., C. Bartling, and K. Baum, *Adulteration of urine samples, discovery and mitigation.* J Appl Life Sci Int, 2018. **16**: p. 1-8.
39. 39. Cuypers, E. and R.J. Flanagan, *The interpretation of hair analysis for drugs and drug metabolites.* Clinical Toxicology, 2018. **56**(2): p. 90-100.
40. 40. Soares Nunes, L.A., S. Mussavira, and O. Sukumaran Bindhu, *Clinical and diagnostic utility of saliva as a non-invasive diagnostic fluid: a systematic review.* Biochemia medica, 2015. **25**(2): p. 177-192.
41. 41. Kiang, T.K. and M.H. Ensom, *A qualitative review on the pharmacokinetics of antibiotics in saliva: implications on clinical pharmacokinetic monitoring in humans.* Clinical pharmacokinetics, 2016. **55**: p. 313-358.
42. 42. Bertrand, P.G., et al., *Toxicovigilance systems and practices in Africa.* Toxics, 2016. **4**(3): p. 13.
43. 43. Tettey, J.N., et al., *Emergence, diversity, and control of new psychoactive substances: a global perspective.* New Psychoactive Substances: Pharmacology, Clinical, Forensic and Analytical Toxicology, 2018: p. 51-67.