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Review Article

Psychoactive Substances: Analytical Strategies for the Identification of Designer Drugs in Forensic and Clinical Contexts

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Abstract

Introduction: Designer drugs, or novel psychoactive substances (NPS), are synthetic analogues of controlled drugs engineered to mimic their pharmacological effects while evading legal regulation. Their rapid emergence and global distribution pose major challenges to public health, law enforcement, and analytical laboratories due to their unpredictable effects and complex chemical variability.

Methods: This review compiled and analyzed recent literature on the classification, pharmacology, abuse patterns, and analytical detection of designer drugs. Key instrumental techniques such as gas chromatography–mass spectrometry (GC-MS), liquid chromatography–tandem mass spectrometry (LC-MS/MS), and nuclear magnetic resonance (NMR) were evaluated alongside novel sensor-based technologies. Relevant case studies were examined to highlight clinical and forensic implications.

Findings: The major classes of designer drugs include synthetic cathinones, cannabinoids, benzodiazepines, phenidate derivatives, and dissociatives. Traditional analytical methods provide high sensitivity and selectivity but face challenges like matrix effects, derivatization needs, and limited on-site applicability. Emerging sensor technologies, including molecularly imprinted polymers and aptamer-based biosensors, offer rapid and portable alternatives for field testing. GC-MS and LC-MS/MS remain the gold standards for confirmatory testing, while innovative nano-enabled sensors show promise for real-time detection and point-of-care diagnostics.

Conclusion: Continuous evolution of designer drugs necessitates adaptable analytical strategies. Integration of advanced sensor platforms with established chromatographic methods and strengthened inter-laboratory validation can enhance global surveillance and improve public health responses to NPS abuse.

Keywords: Designer drugs, Novel psychoactive substances, Analytical detection, Sensor technology, Forensic toxicology

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Introduction

Designer drugs are synthetic substances engineered to mimic the effects of controlled drugs while evading legal restrictions by modifying their chemical structures. These compounds are often derivatives of scheduled substances and are sold illicitly to bypass regulatory frameworks. The continuous development and illegal introduction of new designer drugs into the market present a significant challenge for detection and enforcement. Their rapidly evolving nature complicates the implementation of consistent and reliable analytical screening methods. As a result, designer drugs pose an increasing threat to public health and present regulatory dilemmas for law enforcement and policymakers. The term "designer drug" was coined by Dr. Gary Henderson, a pharmacologist at the University of California, Davis, to describe structurally altered analogues of illegal drugs created to circumvent existing laws. These substances are typically developed to preserve or enhance the pharmacological effects of known drugs while remaining outside the scope of legal control. Although this term generally refers to compounds that have never received FDA approval, some are medically licensed in certain countries, blurring their classification.[1] The internet has significantly contributed to the spread of designer drugs by enabling easy distribution and access to information. Their evolving usage patterns and chemical variants make regulation challenging and complicate efforts to protect public health. These substances span various pharmacological classes, including stimulants, sedatives, dissociatives, cannabinoids, and psychedelics. Many designer drugs evade standard drug screenings, and their health risks remain poorly understood. This highlights the urgent need for comprehensive drug analysis, especially for healthcare professionals managing opioid use and substance abuse disorders. This study aimed to provide an overview of available designer drugs and their clinical

implications.

Classification and Pharmacology

Stimulant designer drugs

Stimulant designer drugs are synthetic substances designed to mimic the effects of illegal stimulants like cocaine and amphetamines. Common types include β-keto amphetamines, methylenedioxy derivatives, and piperazines, often marketed as "bath salts" under names like Cloud Nine or Vanilla Sky. These drugs act as monoamine releasers, boosting neurotransmitters like serotonin and norepinephrine, leading to euphoria, alertness, and potential neurotoxicity. Despite being banned in many countries, they remain readily available online and in headshops. Side effects include anxiety, mydriasis, bruxism, and, in severe cases, paranoia and cardiovascular complications. Their long-term health impacts are still largely unknown, raising significant public health concerns.

Amphetamines

Amphetamines that are outdated are used for both medical and recreational purposes. Many amphetamine designer drugs are being made available without proper acceptance for medical uses. MDA is the most popular amphetamine designer drug, classification and analytical methods for the detection of amphetamines are summarized in Table 1.

Derivatives of Cathinone and Pyrovalerone

By-products of the β-ketoamphetamine cathinone are cathinone designer drugs. This alkaloid is naturally found in the leaves of the *Catha edulis* plant.[10] Although certain related compounds have been recognized for years, the broad use of synthetic cathinones has emerged only in recent times.[11, 12] Although the medical potential of certain other synthetic cathinones, mostly antidepressant or anorectic drugs, has been investigated, only a small number of these drugs were marketed due to worries about abuse. The analytical methods employed for the identification and quantification of these synthetic cathinones in various biological and forensic matrices are summarized in Table 2. The table highlights commonly used chromatographic and spectroscopic techniques along with their respective advantages and limitations for reliable detection. In addition, the chemical structures of important synthetic cathinone derivatives are illustrated in Figure 1, providing a comparative understanding of their structural similarities and substitutions responsible for variations in pharmacological and toxicological properties. These structural modifications significantly influence their potency, metabolism, and analytical behavior during detection and characterization studies.

Table 1. Analytical Methods for the Detection of Amphetamines[2]

Designer Drugs	Matrices	Techniques	Limitations
3,4-methylenedioxyamphetamine (MDA)	Serum or Urine	GC-MS[3]	Requires derivatization to enhance volatility and chromatographic behavior, adding complexity and potential for artifacts.
Methamphetamine Hydrochloride	Drug Crystals	GC-MS[4] GC-FID[5]	GC-MS -Thermal decomposition/artifact formation at the injector/during sample vaporization. GC-FID Crystal meth often contains other substances—cutting agents, solvents, by-products from its synthesis—which may affect the flame response, retention times, or cause overlapping peaks, reducing accuracy.
Methamphetamine	Synthesis	HPLC GC-MS[6, 7] NMR	HPLC Limited selectivity without specific detectors, leading to possible co-elution of impurities. GC-MS Requires derivatization for thermally labile methamphetamine derivatives, increasing analysis complexity. NMR Low sensitivity for trace-level detection, limiting its use for impurity profiling in synthesis samples.
Methoxy Methyl Methamphetamines	Synthesized Standards	GC-MS[8]	Some regioisomeric methoxy-methyl methamphetamines have essentially identical mass spectra under EI-GC-MS, making it impossible to discriminate between them without derivatization or additional techniques.
5,6-methylenedioxy-2-aminoindane; MDAI	Urine	GC-MS[9]	Without derivatization, 5,6-MDAI (and isomeric aminoindanes) give essentially identical mass spectra and co-elute on many GC stationary phases, making it difficult to distinguish and quantify reliably in urine.

Table 2. Detection Methods of Cathinones and Pyrovalerone Derivatives

Designer Drugs	Matrices	Techniques	Limitations
3,4-methylenedioxypyrovalerone (MDPV)	Research Standards	GC-MS[13, 14]	Co-elution and very close RTs make it difficult to distinguish some isomeric cathinones even if mass spectra differ slightly.
5-PPDI	Analytical Sample	FTIR[15]	Spectral overlaps in complex matrices makes distinguishing signals of 5-PPDI from similar functional groups difficult.
N-butylhexedrone	Drug Powder	GC-MS[16]	Poor discrimination of positional isomers of cathinones, since they can fragment similarly, giving non-specific mass spectra.
Methylenedioxy pyrovalerone (MDPV)	Human Urine	LC-MS[17]	Ion suppression in urine from endogenous matrix components can reduce the signal of MDPV.
Pyrovalerone and its hydroxylated metabolite	Rat Plasma / Urine	GC-MS[18, 19]	It has limited sensitivity, so low concentrations may not be detected reliably.

Piperazine derivatives

Piperazines are characterized by a six-membered ring containing two nitrogen atoms opposite each other. They have a range of applications, including use as anthelmintics, antihistamines, antidepressants, antipsychotics, and as curing agents in epoxy resins and polymers.[20] However, certain piperazine derivatives—such as 1-benzylpiperazine (BZP)—are misused for their psychoactive effects and are often marketed as "party pills". These compounds produce stimulant and hallucinogenic effects similar to those of amphetamines, leading to confusion in both human and animal subjects regarding their pharmacological classification. Piperazines abused for recreational purposes are generally categorized into two subclasses: benzylpiperazines, including BZP and its derivatives, and phenylpiperazines, such as 1-(3,4-methylenedioxybenzyl) piperazine. These synthetic compounds are structurally related to piperazine and are frequently sold as alternatives to MDMA or amphetamines due to their comparable stimulant profiles, and their detection methods. Table 3 summarizes the commonly employed analytical techniques used for the identification and quantification of piperazine derivatives in pharmaceutical, biological, and forensic samples, whereas Figure 2 illustrates the chemical structures of major piperazine analogs associated with recreational abuse.

Phenidate Derivatives

Methylphenidate, a piperidine-based prescription drug, has led to the creation of designer drugs with variations in the phenyl ring and carbon side chain length.[23] It enhances cognition and induces euphoria, and due to its similar effects to cocaine, methylphenidate derivatives are sometimes used as cocaine substitutes when inhaled. Methylphenidate and its derivatives primarily inhibit the norepinephrine (NET) and dopamine (DAT) transporters without acting as substrates. While they may weakly interact with the serotonin transporter (SERT) and adrenergic receptors, these interactions are unlikely to significantly affect their psychoactive properties. The techniques for analytical detection of phenidate derivatives are summarized in Table 4. The table highlights various chromatographic and mass spectrometric techniques employed for sensitive and selective detection, along with their associated analytical limitations and challenges during sample analysis.

Sedative designer drugs

Benzodiazepines, selective benzodiazepine receptor

Table 3. Detection of Piperazine Derivatives

Designer drugs	Techniques	Limitations
Piperazine	FTIR[21]	Strong water vapour absorption overlaps with N-H/amine bands and protein/lipid regions, making the detection difficult.
1-Benzyl-Piperazine	GC-MS[22]	LOD in human plasma by the derivatization-free GC-MS method is relatively high, so lower concentration exposures may go undetected.

Table 4. Techniques for Analytical Detection of Phenidate Derivatives

Designer drugs	Matrices	Techniques	Limitations
Methylphenidate (MPH) hydrochloride	Urine	LC-MS/MS[24]	Matrix effect in urine can distort quantitation unless well-controlled with internal standards.

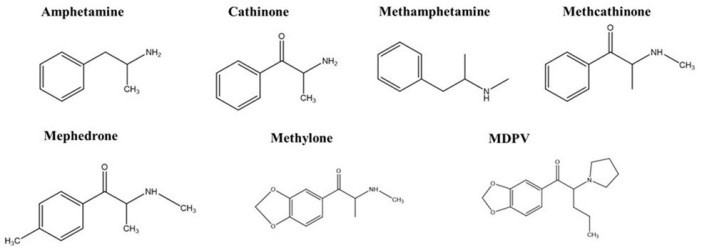

Figure 1. Chemical structures of amphetamine and cathinone derivatives

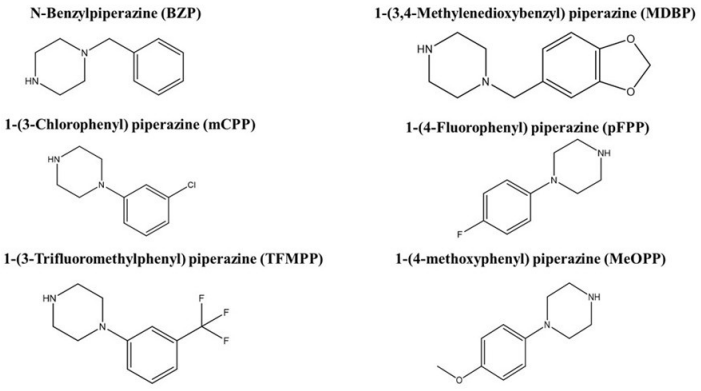

Figure 2. Chemical structure for piperazine derivatives

subtype agonists, and barbiturates are all sedatives that are commonly prescribed for anxiety or insomnia. Due to the likelihood of misuse and abuse, these sedatives are controlled substances. Self-medication (chemical coping) of psychological symptoms in forms not approved by the prescriber, most often as dose escalation leading to demands for early refills, is referred to as misuse. Sedatives are misused for their euphoric effects, which can lead to harmful outcomes. Sedative designer drugs show a wide variety of side effects, including light-headedness, reduced alertness, constricted pupils, suppression of central nervous system activity, slowed or impaired breathing, fluid buildup in the lungs, oxygen deficiency, and a decreased heart rate, and their detection methods are depicted in Table 5 and Figure 3. Table 5 summarizes the analytical techniques commonly employed for the detection and confirmation of sedative designer drugs in biological and forensic samples, while Figure 3 illustrates the chemical structures of major sedative derivatives associated with abuse and misuse.

Dissociative designer drugs

Because of their different pharmacological effects, dissociative agents are valued in medicine. Recreational drug users are generally aware of these pharmacological effects. At anesthetic doses, the dissociative agent ketamine produces analgesia without causing cardiovascular or respiratory depression—a property that distinguishes it from conventional anesthetics. However, its use is associated with adverse effects such as agitation, confusion, disorientation, dissociation, hallucinations, memory loss, nystagmus, slurred speech, excessive sweating, high blood pressure, rapid heart rate, and impaired kidney function.

Synthetic cannabinoids

Table 5. Identification of Synthetic Opioids

Designer drugs	Techniques	Limitations
Morphine-3-glucuronide (M-3-G)	HPLC[25, 26]	Co-elution or interference from endogenous compounds can reduce specificity in HPLC assays unless extensive sample cleanup is used.
Fentanyl	GC-MS/MS[27]	Sample pretreatment is often complex and time-consuming in GC-MS for biological matrices, reducing throughput.

Synthetic cannabinoids are scattered on a variety of herbal or dried plant matter for the purposes of being smoked to achieve a "high." These goods are sold online and at convenience stores, liquor stores, smoke shops, 'head shops', and gas stations. Although cannabis plants do not produce synthetic cannabinoids and are not equal to tetrahydrocannabinol (THC), they share receptors with THC.[28] These compounds form a large and diverse group that exhibits certain similarities to THC. Similar to cannabis, SCPs are widely used by young people who want to "get high." SCP use can deliver an assortment of actual impacts. Cardiovascular and GI impacts are normal, and conceivably genuine renal (intense kidney injury) and neurological (seizures) impacts have likewise been noticed.[29] Discoveries from case reports demonstrate that SCPs can deliver impacts past intense inebriation; resistance and withdrawal manifestations might be noticed after delayed use. These starters recommend that reliance might be related to long-term SCP use. The commonly used analytical techniques for the identification of synthetic cannabinoids and their associated limitations are summarized in Table 6.

Analytical Methods for the Detection of Designer Drugs

Designer benzodiazepines, amphetamines, cathinones, and piperazines are screened and confirmed in laboratory testing using gas chromatography coupled with mass spectrometry (GC-MS) or liquid chromatography combined with tandem mass spectrometry (LC-MS/MS). A second aliquot is used to confirm all presumed positive specimens before reporting positive findings. The scientifically validated analytical techniques employed for the detection and confirmation of these designer drugs are summarized in Tables 7. These tables provide an overview of the commonly used chromatographic methods, detection principles, and their applicability in forensic and

Table 6. Identification of Synthetic Cannabinoids

Designer drugs	Techniques	Limitations
Synthetic Cannabinoids	LC-MS[30] GC-MS	Ion suppression from co-eluting endogenous compounds can reduce sensitivity and quantification accuracy in complex biological matrices.

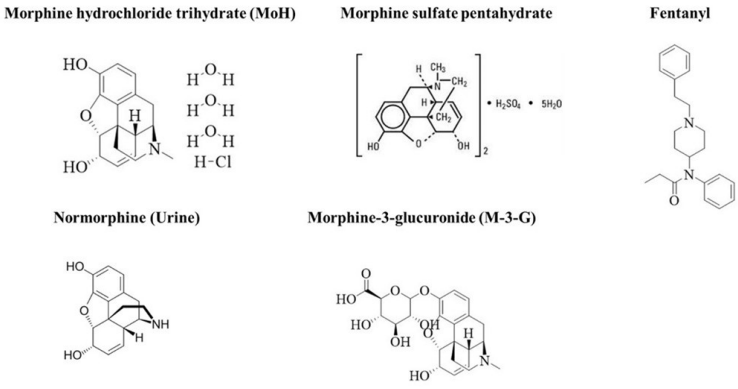

Figure 3. Chemical structures of opioids and their metabolites

Table 7. Detection of Aryl Cyclohexamine and Diaryl Thylamine Designer Drugs

Designer drugs	Matrices	Techniques	Limitations
Ketamine and Norketamine	Urine Rat serum	LC-MS[31, 32] GC-MS[33, 34]	Ion suppression from co-eluting endogenous urine matrix compounds can lower the signal. *GC-MS* Some require derivatization to improve volatility and detection, which adds steps and can lead to losses or variability.

toxicological investigations for accurate identification of novel psychoactive substances.

Metabolite Profiling and Inter-Laboratory Validation of NPS

Metabolite Profiling of NPS

Metabolite profiling refers to the systematic identification and quantification of metabolites generated after biotransformation of NPS in the human body. Since many NPS are structurally modified to evade legal control and standard detection methods, direct identification of the parent compound is often tricky. Therefore, metabolite profiling provides critical insights for both toxicological assessment and analytical method development.

Detecting NPS Consumption

- Confirmation of intake: Many NPS are rapidly metabolized, and their parent compound may be undetectable in biological matrices such as urine, serum, or plasma. Forensic scientists can confirm recent consumption by studying the metabolite profile even when the parent drug is absent.
- Unique biomarkers: Certain metabolites serve as specific markers that distinguish one NPS from another, improving detection reliability compared to immunoassays, which often lack specificity.
- Extended detection window: Some metabolites persist longer in the body than the parent drug, providing a broader timeframe to identify exposure.

Understanding Metabolic Pathways

Metabolite profiling of novel psychoactive substances (NPS) provides critical insights into their biotransformation pathways, revealing how these compounds undergo phase I reactions, such as oxidation, reduction, and hydrolysis, as well as phase II reactions, including conjugation with glucuronide, sulphate, and other groups. Understanding these metabolic routes is essential for predicting pharmacological and toxicological effects, as metabolites may retain biological activity or, in some cases, exhibit greater toxicity than the parent compound. Additionally, metabolite profiling uncovers inter-individual variations in metabolism, which can result from genetic polymorphisms in enzymes such as CYP450, drug-drug interactions, or organ impairments, ultimately influencing the intensity, duration, and overall risk profile of NPS use.

Developing Analytical Methods

Metabolite profiling plays a pivotal role in the development of targeted analytical assays. Once primary compound metabolites are identified, techniques such as LC-MS/MS or GC-MS can selectively detect these metabolites, rather than relying solely on the parent substance. This approach also facilitates the synthesis and validation of reference standards for analytical laboratories, a critical need given the rapid emergence and turnover of novel psychoactive substances on the illicit market. Furthermore, characterizing metabolite patterns enables inter-laboratory validation, ensuring that standardized detection methods are consistent and reliable across forensic and clinical settings. High-resolution mass spectrometry (HRMS) further benefits from metabolite profiling, allowing comprehensive screening of unknown compounds and detecting both expected and previously unrecognized metabolites.

Approaches

In Vivo Studies

Administering NPS to animal models and analyzing biological samples (e.g., urine, plasma) to identify metabolites.

Example

A study on synthetic opioids like morphine and fentanyl in murine models revealed alterations in energy metabolism and disrupted catecholamine biosynthesis pathways.[35]

In vitro Studies

Using human liver microsomes or hepatocytes to simulate metabolic processes and identify metabolites.

Analytical Techniques

Liquid Chromatography–High Resolution Mass Spectrometry (LC-HRMS)

Liquid Chromatography (LC) separates analytes using a liquid mobile phase and a solid stationary phase. At the same time, High-Resolution Mass Spectrometry (HRMS) provides highly accurate mass measurements and satisfactory resolution of ions (e.g., Orbitrap, Q-TOF). The system can operate in full-scan mode for non-targeted analysis, in data-dependent/data-independent MS/MS modes for structural elucidation, and in targeted mode for specific compounds. Ionization is most achieved through Electrospray Ionization (ESI), although other ion sources may be employed. Additionally, polarity switching enables the detection of both positive and negative ions in a single run.

Advantages for metabolite profiling of NPS/xenobiotics

High sensitivity and mass accuracy allow for the detection of metabolites at very low concentrations and enable the precise determination of elemental compositions, which is particularly valuable for identifying unknown or structurally modified NPS. The broad dynamic range of these techniques permits the detection of both highly abundant and trace-level metabolites within a single analysis. Their versatility makes them suitable for analyzing

non-volatile, polar, thermolabile, and high-molecular-weight metabolites that are difficult to measure using GC-based methods. These approaches also facilitate concurrent quantification and discovery, allowing for targeted analysis of known metabolites using reference standards while screening for previously unidentified compounds.

Limitations/challenges

LC-HRMS, while highly versatile, also has certain limitations. Ion suppression from complex biological matrices can affect sensitivity and accuracy, making careful sample preparation essential. Effective chromatographic separation is often required to resolve isomers, since they may share the same mass and cannot be distinguished by mass accuracy alone. In addition, reference standards are frequently unavailable for newly emerging or unknown metabolites, complicating identification and quantification. The technique may also involve longer analysis times and relies on relatively costly instrumentation, limiting accessibility in some laboratory settings.

Examples/studies

- *In vitro characterization of metabolites of furanyl fentanyl* (Fu-F) using human liver microsomes & HepaRG cells with LC-HRMS: 17 Fu-F metabolites identified; multiple metabolic pathways postulated.[36]
- *Simultaneous determination of 40 novel psychoactive stimulants in urine* by LC-HRMS; quantifies multiple NPS and some metabolites.[37]

Gas Chromatography–Mass Spectrometry (GC-MS)

Gas Chromatography (GC) works by vaporizing analytes and separating them according to their volatility and interactions with the stationary phase. The separated compounds are then detected by Mass Spectrometry (MS), typically using electron ionization (EI) or chemical ionization (CI). Since many analytes, particularly polar compounds, are not naturally volatile or thermally stable, they often require derivatization (e.g., silylation, methoximation) to enhance volatility, stability, and detectability.

Advantages of metabolite profiling

GC-MS offers high separation power and resolution, resulting in sharp chromatographic peaks with excellent reproducibility. It generates characteristic fragmentation patterns, particularly under electron ionization (EI), which can be matched against comprehensive spectral libraries such as NIST, Fiehn, and Wiley, making it highly effective for identifying unknown compounds. The technique is especially well-suited for volatile and semi-volatile analytes and can also be applied to small polar metabolites once derivatized. Moreover, GC-MS offers reliable quantification with good accuracy and reduced matrix interference for certain classes of compounds.

Limitations/challenges

GC-MS is limited to compounds that are volatile, thermally stable, or made amenable to analysis through derivatization. Thermolabile or highly polar metabolites often degrade or fail to volatilize, reducing detection efficiency. The need for derivatization also complicates the workflow, introducing risks of artifacts or incomplete reactions. Additionally, sample preparation is generally more labor-intensive than other analytical techniques. As a result, GC-MS may overlook metabolites that are non-volatile, strongly polar, or of high molecular weight, restricting its applicability in comprehensive metabolite profiling.

Detection gaps

Less suitable for non-volatile, strongly polar, or high-molecular-weight metabolites, which may remain undetected.

Examples/studies

Metabolomics by GC-MS: Combined targeted and untargeted profiling of small molecules (< 650 Da) in human body fluids. This work shows that GC-MS, with derivatization, can identify/quantify over 200 compounds in fluids like urine/plasma.[38]

Nuclear Magnetic Resonance (NMR) Spectroscopy

In NMR analysis, a sample—whether in liquid, solution, or occasionally solid form—is placed within a strong magnetic field. Nuclei such as 1H, 13C, and others absorb radiofrequency energy, producing signals that reflect their specific chemical environments.

Structural information can be obtained through one-dimensional (^1H) or advanced two-dimensional techniques (e.g., COSY, HSQC, HMBC). Additionally, quantitative NMR (qNMR) enables direct measurement of metabolite concentrations when appropriate calibration is applied.

Advantages of metabolite profiling

NMR is highly effective for structural elucidation, making it particularly valuable for characterizing unknown metabolites by providing insights into stereochemistry, molecular connectivity, and conformations. The technique is highly reproducible, relatively non-destructive, and generally requires minimal sample preparation compared to derivatization steps in GC or complex separations in other methods. In some cases, it can also be used for quantification without the need for external reference standards since signal intensity is directly proportional to the number of nuclei present, as in quantitative NMR (qNMR). While less sensitive than MS-based approaches, NMR is especially suitable for high-abundance metabolites and is widely applied in extensive cohort studies where consistent, reproducible data are essential.

Limitations/challenges

Despite its strengths, NMR has some important limitations. Its relatively low sensitivity means metabolites at very low concentrations (ng–µg/L) may go undetected. In complex mixtures, overlapping signals can make data interpretation

challenging, and distinguishing isomers often requires high-field instruments or advanced two-dimensional techniques. Also, NMR systems are expensive to acquire and maintain, and the detailed structural elucidation process can be slower than mass spectrometry-based methods, limiting their routine use in high-throughput analyses.[39]

Examples/studies

- *NMR spectroscopy for metabolomics research* (a review) discusses how NMR complements MS methods: Ease of sample preparation, high reproducibility, but sensitivity is lower (often 10- to 100-fold).[40]

Inter-Laboratory Validation

To ensure the broader applicability of metabolite profiling data, it is crucial to maintain consistency and reliability across different laboratories. Inter-laboratory validation plays a key role by demonstrating reproducibility of results, promoting standardized protocols and reference materials, and enabling the data integration from multiple sources for more comprehensive analysis.

Notable Studies

GC-MS Profiling

An inter-laboratory study assessed the reproducibility of untargeted metabolomics using human plasma samples. The results showed variability in metabolite *annotations and quantifications, highlighting the need for standardized protocols.*[41]

Proficiency Testing

Developing quartet metabolite reference materials has been recommended to enhance inter-laboratory proficiency in metabolomics. These materials serve as benchmarks for validating analytical methods.[42]

Data Integration Challenges

A study involving 12 laboratories analyzed identical samples to evaluate data integration capabilities. The findings indicated that while some metabolites showed consistent quantification across labs, others exhibited significant discrepancies due to factors such as peak identification errors and differences in instrumentation.

Recent Advances and Tools

In Silico Metabolism Prediction

Tools like GLORYx, BioTransformer 3.0, SyGMa, and MetaTrans are being evaluated for their ability to predict NPS metabolism, aiding in the identification of potential metabolites before experimental studies.[43]

Automated Structure Elucidation

Deep learning models are being developed to predict MS/MS spectra of NPS, facilitating the identification of novel substances and their metabolites.

Clinical Case Studies and Toxicity

Case study of stimulant designer drugs

A new generation of designer drugs that produce effects like those of stimulants like cocaine/amphetamines and ecstasy (MDMA [3,4-methylenedioxy-N-methamphetamine]) is being marketed to recreational drug users as "bath salts" and "plant food." In the instance of a patient who inhaled Cristalius, a bath salt. A male soldier, aged 22 years, was brought to the emergency room with tachycardia, anxiety, bewilderment, and syncope. He claimed to have snorted one gram of Cristalius the night before. Creatine kinase levels of 668 U/L, serum creatinine levels of 1.35 mg/dL, and troponin levels of 0.516 ng/mL were among the noteworthy laboratory findings. Mephedrone and a synthetic cathinone produced from the Khat plant are the main components suggested in these items. The projected effects include ecstasy, empathic connection, mood enhancement, and increased sensory perception, with decreased inhibition. Unwanted sympathomimetic side effects may involve elevated blood pressure, rapid heart rate, chest discomfort, excessive sweating, pupil dilation, seizures, teeth grinding, and headaches. Additionally, neuropsychiatric manifestations can include restlessness, heightened anxiety, paranoid thoughts, shaking, and difficulty sleeping.

Case study of synthetic cathinones

A 31-year-old male with a history of chronic substance abuse was brought to the emergency department following the injection of an unidentified hallucinogenic substance, reportedly recommended by his dealer. On initial evaluation, he exhibited symptoms including rapid heartbeat, palpitations, dilated pupils, shortness of breath, dizziness, headache, and nausea, all of which gradually improved during his stay. Despite medical advice, he left the hospital on his own. The following day, he returned to the ER accompanied by six police officers. According to reports, he had become increasingly aggressive and confused, threatening his grandmother and causing damage to household items in a state of rage. Due to his refusal to cooperate, law enforcement used pepper spray, rubber bullets, and a taser to subdue him before transporting him to the hospital in restraints. At the ER, ketamine and propofol were administered to allow for a proper medical evaluation. During his psychiatric assessment, the patient disclosed that he had injected synthetic substances intravenously over the previous two days. His aggressive behavior resolved within a few hours, and no signs of underlying psychiatric disorders were detected by the evaluating psychiatrist.

He was discharged from the hospital but returned approximately a month later, stating that he had been experiencing withdrawal symptoms for the past five days. He reported widespread body pain, trouble sleeping, auditory hallucinations, and heightened anxiety. Ultimately, he was referred to a psychiatric facility to undergo his 21st attempt at detoxification.

Case study of sedative designer drugs

An artificial analog of fentanyl known as Acetyl fentanyl is like heroin in colour and consistency. We present a case of lethal intoxication caused by acetyl fentanyl insufflation. Acetyl fentanyl levels in his blood were 270 ng per mL, and his death was concluded as accidental. He was snoring loudly for at least 12 hours before he passed away, and naloxone therapy and hospitalization during this time might have saved his life. According to this viewpoint, his death could have been avoided. This example illustrates the small margin between the lethal dosage (LD50) and the effective dosage (ED50), along with the potential for fatal outcomes associated with excessive drug dosage. The example should also make medical professionals more aware of the efficacy of naloxone and the need to implement a thorough toxicological analysis system while taking the potential usage of "designer drugs" into consideration.[44]

***Case study* of dissociative designer drugs**

John Huffman is a professor emeritus of chemistry at Clemson University in South Carolina. After earning a doctorate in chemistry from Harvard University, Huffman joined the faculty at Clemson and devoted most of his career to teaching chemistry at both undergraduate and graduate levels, while actively maintaining a research program funded by grants, which is the typical path taken by academic scientists. His primary research focus was on creating new cannabinoids, which are medications that have some characteristics with cannabis' primary psychoactive ingredient, 9-tetrahydrocannabinol (THC). In recent years, Huffman has begun receiving calls from law enforcement, military personnel, and concerned parents—a situation that has persisted even after his retirement at the end of September 2010. The source of their concern was JWH-018, a synthetic cannabinoid that Huffman had originally designed and synthesized in his lab. Forensic experts had detected this compound in herbal products sold online as incense. Although marketed as incense (under names like Spice Gold, Spice Diamond, Purple Haze, K2, and Skunk), these herbal mixtures were reportedly being smoked by users to experience effects like those of marijuana.[45]

Treatment of Designer Drug Addiction

Raising awareness among healthcare providers and educating patients are crucial public health strategies to address the emerging threat of designer drugs. Early intervention through simple advice may help, but often falls short, as many users are ambivalent about change. Clinicians should adopt a nonjudgmental, empathetic approach that respects patient autonomy while providing accurate information about the risks of designer drugs to support informed decision-making. Engaging patients in collaborative problem-solving and emphasizing personal responsibility fosters motivation for recovery without blame. While data on specific treatments is limited, sustained recovery typically requires long-term, comprehensive care similar to other substance use disorders—incorporating individual and group counselling, behavioral therapies, and support groups, with family involvement especially important for the youth. Unfortunately, there is a lack of pharmacologic options specifically for managing designer drug use.

Prevalence and Usage Trends

Designer drugs, or novel psychoactive substances (NPS), are synthetic compounds created to mimic-controlled drugs while avoiding legal bans. Use is most common among young male adults, especially those with lower education and income levels, and is prevalent in nightlife settings like clubs and festivals. High-risk groups include cannabis users, college students, and partygoers. Misperceptions of safety and legal ambiguity increase their appeal, despite serious risks such as toxicity, psychological issues, and death. Polysubstance use and the unknown content of these drugs complicate treatment. Monitoring trends is vital for effective prevention and public health strategies.[46]

New Developments and Potential Paths

Designer drugs, sometimes referred to as novel psychoactive substances (NPS), are artificial substances created to resemble the effects of substances under control while evading legal limitations. These substances' environment is always changing, bringing with it new difficulties and factors to consider.

Emerging Trends

The landscape of designer drug use is rapidly evolving, presenting new challenges for public health and regulatory authorities. First, there is a marked proliferation of novel compounds, with new substances frequently entering the market. This constant emergence complicates detection, regulation, and timely intervention efforts. Second, the distribution of designer drugs has increasingly shifted to digital platforms, particularly social media and encrypted messaging apps, where dealers use coded language and emojis to evade law enforcement. This mode of distribution enhances accessibility, especially among the youth. Third, polysubstance use—either the simultaneous use of multiple designer drugs or their combination with other illicit substances—is becoming more prevalent, heightening the risk of adverse health outcomes and complicating clinical management. Lastly, designer drugs are no longer confined to specific regions; they are now globally distributed. For instance, substances like "pink cocaine" have expanded from Latin America into nightlife scenes across Europe and the UK, contributing to an increased incidence of drug-related harms. These trends underscore the urgent need for adaptive public health strategies and global cooperation in surveillance and control.

Future Directions in Addressing Designer Drugs

Effectively responding to the challenges posed by designer drugs requires a multidimensional strategy. Advancements in analytical technologies are urgently needed to enable rapid detection and monitoring of emerging substances. Regulatory frameworks are being adapted to become more agile and globally coordinated, allowing for timely

updates to controlled substance lists. Public health efforts are increasingly focused on harm reduction, education, accessible treatment services, and the development of safer therapeutic alternatives, particularly in psychedelic-assisted mental health care. Continued research is vital for understanding the pharmacology, toxicity, and epidemiology of these substances, with robust surveillance systems informing evidence-based policies and interventions.

Among the innovative analytical solutions, sensor-based technologies are gaining significant attention for their potential in the rapid, sensitive, and on-site detection of illicit drugs, marking the next frontier in tackling this complex issue.

Sensors for Illicit Drug Analysis

Drug abuse has serious negative effects on one's health, and the danger varies depending on the user and the substance. Consequently, these medications must be highly sensitively and selectively identified at their cutoff level. This section describes the properties of several medications, with an emphasis on tetrahydrocannabinol (THC), cocaine (COC), opiates (OPs), amphetamines (AMPs), and methamphetamine (M-AMPs), as well as benzodiazepines (BZDs). It also discusses technological advancements in the development of optical and electrochemical sensors, along with their analytical performance features.

Tetrahydrocannabinol

Cannabis, derived from *Cannabis sativa*, *indica*, and *ruderalis*, contains psychoactive cannabinoids such as THC, cannabidiol, and cannabinol, which can induce effects like euphoria, anxiety, and cognitive impairment. Δ9-tetrahydrocannabinol (THC) is the primary psychoactive component, and its detection in biological or environmental samples is critical for controlling illicit use. This underscores the need for advanced sensing technologies capable of accurately identifying THC presence.[47]

Molecularly imprinted polymers (MIPs) are artificially engineered polymers synthesized by polymerizing functional monomers in the presence of a template molecule. Following polymerization, the template is removed, leaving behind specific binding cavities that are complementary in size, geometry, and chemical functionality to the target analyte. These imprinted sites function as synthetic recognition elements, capable of selectively rebinding the target molecule through defined interactions such as hydrogen bonding, electrostatic attraction, van der Waals forces, and hydrophobic interactions, closely mimicking the specificity of natural antibody–antigen recognition.[48] Owing to their high stability, reusability, and cost-effectiveness, MIPs have been widely applied in separations, catalysis, drug delivery, and particularly in molecular sensing. Recent advances in sensor technology have integrated MIPs with nanomaterials such as carbon nanotubes (CNTs) to improve analytical performance, where MIPs impart strong target selectivity, and CNTs enhance electrical conductivity to amplify detection signals. For example, an electrochemical sensor combining MIPs and CNTs achieved a 0.18 ng/mL detection limit for THC using differential pulse voltammetry, while a portable platform developed by Lee et al. Electrochemical sensing of cannabinoids using molecularly imprinted polymers (MIPs) and carbon nanotubes are illustrated in Figure 4. The figure depicts a giant magneto resistive (GMR) biosensor integrated with a smartphone interface for saliva-based THC detection, reaching a detection limit of 5 ng/mL and demonstrating the potential of such systems for rapid, on-site drug screening.[49,50]

Cocaine

Cocaine (COC) is a potent, addictive alkaloid derived from the coca plant (*Erythroxylon coca*), commonly used as a local anesthetic due to its vasoconstrictive properties. Its stimulating and euphoric effects rapidly impact the brain and nervous system, especially when administered via injection or inhalation. Peak plasma concentrations can range from 200–600 ng/mL within 30–120 minutes, contributing to its high abuse potential.[53] Chronic use leads to severe health consequences, including paranoia, anxiety, cognitive disorders, seizures, and potentially death, necessitating rapid and accurate on-site detection methods. Among the emerging strategies, aptamer-based biosensors have gained attention as highly specific and sensitive tools for cocaine detection.

Aptamers are short, single-stranded DNA or RNA oligonucleotides that undergo conformational changes upon binding to a target analyte. They act as nucleic acid-based recognition elements capable of selectively binding a wide range of molecules, including proteins, bacterial cells, and metal ions.[54] Through careful selection, aptamers can be engineered with high specificity and affinity for a particular target. The binding event typically induces a structural rearrangement in the aptamer, leading to measurable changes in physicochemical properties, such as electrochemical signals.[55] Aptamers are commonly identified and optimized through the Systematic Evolution of Ligands by Exponential Enrichment (SELEX) process.[56] Electrochemical aptamer-based (E-AB) biosensors exploit both the biorecognition capability of aptamers and electrochemical transduction, enabling real-time

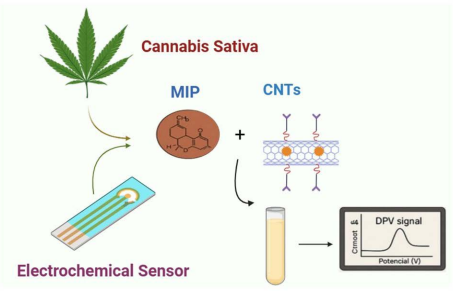

Figure 4. Electrochemical sensing of cannabinoids using molecularly imprinted polymers (MIPs) and carbon nanotubes (CNTs)[51,52]

and potentially in vivo monitoring of analytes. An electrochemical aptamer-based (E-AB) biosensor produces a measurable electrochemical response upon selective target binding in vivo, where the interaction is transduced as a change in the Faradaic current at the electrode surface.[57]

Aptamers—synthetic nucleic acids with high binding specificity—offer a promising alternative to antibodies in biosensor applications due to their low cost, stability, and ease of modification. Their use in conjunction with nanomaterials such as graphene, carbon nanotubes, and quantum dots has significantly improved sensor sensitivity for small molecule detection, including cocaine. These aptamer-based biosensors can provide high selectivity and are well-suited for detecting trace amounts of COC in complex biological samples.[58,59]

One notable advancement is the integration of aptamers with nanopore technology, which measures real-time changes in ionic current caused by analyte interaction. Electrochemical aptamer-based biosensors also benefit from miniaturization using nano- and micro-electrodes, enhancing their detection limits and analytical performance. These innovations support the development of cost-effective, portable devices suitable for commercial use in point-of-care and forensic drug testing scenarios. Figure 5 shows a Cocaine detection using a -hemolysin nanopore and DNA aptamer, where cocaine binding induces aptamer folding and blocks nanopore translocation.

Opioids

Opioids, derived from *Papaver somniferum*, include natural (morphine, codeine), semi-synthetic (oxycodone, buprenorphine), and synthetic variants (fentanyl, diphenyl propylamines). They act on opioid receptors in the brain and nervous system to relieve pain and are also used in treating anxiety, depression, and addiction.[61,62]

Fentanyl

Fentanyl and its analogues are highly potent opioids; carfentanil is 10,000 times stronger than morphine. Overdose symptoms include blue lips, respiratory distress, and chest rigidity, often leading to death. Electrochemical sensors, like the "Lab-on-a-glove" system with MWCNT/SPCE electrodes, can detect fentanyl at concentrations as low as 10 μM, offering real-time monitoring via a smartphone. Due to their danger and rising misuse, rapid detection tools for fentanyl analogues are urgently needed.[63]

Amphetamine and Its Analogues

Amphetamines stimulate dopamine release, enhancing mood and alertness. Despite wide use, even low levels pose health risks, necessitating fast, reliable detection. Traditional spot tests, although commonly used, often lack the accuracy and sensitivity required for dependable screening. To overcome these limitations, nanomaterial-based biosensing strategies, particularly those utilizing aptamer-functionalized gold nanoparticles (GNPs), have gained prominence.

Gold nanoparticles (GNPs) function effectively as nanozymes owing to their strong peroxidase-mimicking activity.[64,65] Their reversible interaction with single-stranded DNA (ssDNA) makes them particularly suitable for aptamer-based sensing strategies.[66] This property was rapidly recognized and extensively explored for biosensing applications. The sensing mechanism relies on the nonspecific adsorption of analyte-specific aptamers onto the GNP surface, which blocks the nanoparticles' catalytic activity.[67] When the corresponding target analyte is introduced, the aptamers preferentially bind to their target molecules and detach from the GNPs, thereby exposing the nanoparticle surface and restoring its intrinsic nanozyme activity.[68] Advanced nanozyme-based aptamer sensors using graphene oxide and AuNPs now enable sensitive, rapid detection, down to 28.6 ng/mL for methamphetamine in under one minute, via a colorimetric response.[69-71] Table 8 presents the evolution of analytical techniques, highlighting the transition from traditional methods to modern emerging approaches.

Future Directions in Addressing Designer Drugs

Effectively responding to the challenges posed by designer drugs requires a multidimensional strategy.[75] Advancements in analytical technologies are urgently needed to enable rapid detection and monitoring of emerging substances. Regulatory frameworks are being adapted to become more agile and globally coordinated, allowing for timely updates to controlled substance lists.

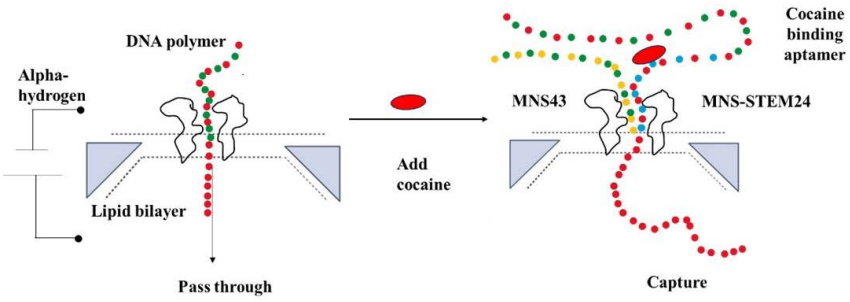

Figure 5. A diagram shows cocaine detection using an α-hemolysin nanopore and a DNA aptamer. Without cocaine, the aptamer remains linear and passes through the nanopore. When cocaine is present, it binds to the aptamer, causing it to fold and block the nanopore, preventing translocation[60]

Table 8. Evolution from Traditional Methods to Modern Emerging Techniques

Method	Advantages	Disadvantages
Color/Spot Tests (Marquis, Scott, Ehrlich)	-Rapid, simple, low cost. -Suitable for on-site presumptive screening.	-Poor selectivity → false positives/negatives -Not quantitative[72].
Thin Layer Chromatography (TLC)	-Easy to perform, inexpensive. -Can screen multiple drugs simultaneously	-Limited resolution. -Requires confirmatory techniques[73].
Gas Chromatography (GC)/High Performance Liquid Chromatography (HPLC)	-Reliable separation. -Established in forensic labs	-GC requires derivatization for non-volatile drugs. -Longer prep time, moderate sensitivity[73].
Immunoassays (ELISA, Lateral Flow)	-Rapid, portable, user-friendly. -Suitable for urine/saliva screening	-Cross-reactivity → false positives -Poor at distinguishing analogues. -Limited quantitation
GC–MS/LC–MS/MS	-Gold-standard confirmatory methods. -High sensitivity & specificity (ng/mL–pg/mL). -Detects metabolites & new psychoactive substances	-Expensive instrumentation. -Requires trained personnel. -Not suitable for field use
Capillary Electrophoresis (CE)	-High efficiency. -Small sample volume. -Rapid analysis	-Limited sensitivity unless coupled with MS. -Less widely adopted in forensic labs.
Nanomaterial-based Biosensors (Aptasensors, Nanozymes, SERS)	-High sensitivity. -Portable and cost-effective. -Specificity via aptamer binding	-Early stage of validation. -Matrix effects may affect reliability[74]
Point-of-Care Devices (Microfluidics, Electrochemical, Smartphone-based)	-Real-time, on-site detection. -Minimal sample preparation. -User-friendly	-Lower accuracy vs. LC–MS. -Not yet standardized for forensic use.

Public health efforts are increasingly focused on harm reduction, education, accessible treatment services, and the development of safer therapeutic alternatives, particularly in psychedelic-assisted mental health care. Further research is vital to understanding the pharmacology, toxicity, and epidemiology of these substances, with robust surveillance systems informing evidence-based policies and interventions.[76]

Conclusion

Techniques for identifying designer drugs in biological fluids or analyzing designer drug-related powders and pills are always being developed. Novel approaches to designer drug analysis are being investigated. The format of the present analysis could be used to determine the atomic structures of various mixes. This work provides data on the analysis of designer drugs to assist chemists in their identification.

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Authors' Contribution

Conceptualization: Danta Sreesahithi.
Data Curation: Nalanda Revu.
Investigation: Danta Sreesahithi, Nalanda Revu.
Methodology: Danta Sreesahithi.
Resources: Danta Sreesahithi.
Supervision: Nalanda Revu.
Validation: Nalanda Revu.
Visualization: Kushita Neduri.
Writing–Original Draft: Danta Sreesahithi.

Competing Interests

The authors declared no conflict of interest.

Ethical Approval

The study does not involve experiments on animals or human subjects

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This statement does not apply to this article, as no datasets were generated or analyzed during the present study.

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