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Designer Drugs and Novel Psychoactive Substances: Chemistry, Toxicological Effects, Abuse Trends, and Forensic Challenges

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Abstract: ***Designer drugs or Novel Psychoactive Substances (NPSs) are synthetic compounds developed to mimic the pharmacological effects of controlled substances, but circumventing legal restrictions. The swift appearance of these compounds has become a significant concern to the global public health and forensic science owing to their increasing abuse potential, unpredictable toxicity, and continuous structural modifications. This review article offers a comprehensive overview of designer drugs, covering their classification, chemistry, pharmacological properties, street names, mechanisms of action, physiological and psychological effects, and current trends in abuse. The review also considers their side-effects on the cardiovascular, neurological, renal, hepatic and psychiatric systems including psychosis, hallucinations, aggression, addiction and fatal overdose. It critically analyses current global patterns of abuse, online drug markets and social media driven distribution. The forensic toxicology challenges in connection with detection, identification and interpretation of designer drugs are also reviewed with emphasis on the use of advanced analytical techniques including GC–MS, LC–MS/MS, high-resolution mass spectrometry and emerging AI-assisted forensic approaches. The review highlights the urgent need for more extensive forensic monitoring, regulatory changes, and multidisciplinary strategies to combat the rapidly evolving epidemic of designer drugs.***

Keywords: Designer Drugs, Novel Psychoactive Substances, Synthetic Cannabinoids, Synthetic Cathinones, Forensic Toxicology, Drug Abuse.

I. INTRODUCTION

Novel Psychoactive Substances (NPSs), also known as designer drugs, are an emerging and rapidly expanding group of synthetic compounds that are designed to produce similar pharmacological effects as controlled drugs like cannabis, cocaine, methamphetamine, lysergic acid diethylamide (LSD) and opioids[1], [2]. These substances are deliberately manufactured with minor chemical modifications to skirt the existing legislation on drugs while continuing to have psychoactive effects. The increasing availability, rapid evolution and unpredictable toxicological effects of designer drugs have emerged over the past two decades as a serious global public health and forensic challenge[3][4].

The global NPS market has witnessed rapid growth with the advent of synthetic cannabinoids, synthetic cathinones (“bath salts”), fentanyl analogs, designer benzodiazepines, and hallucinogenic phenethylamines such as the NBOMe compounds. These drugs are often sold illegally on the street, on the Internet, and on dark web marketplaces under the guise of names such as “Spice,” “K2,” “Flakka,” “Molly,” and “legal highs.” Their widespread availability and relative low cost have led to a tremendous increase in their recreational abuse, particularly in adolescents and young adults[5][6].

Designer drugs carry considerable risk because their pharmacology, metabolism, potency and toxicity are often poorly defined. Many are highly active at cannabinoid, serotonergic, dopaminergic, and opioid receptors and have serious physiological and psychological effects including hallucinations, psychosis, cardiovascular toxicity, respiratory depression, seizures, renal injury, violent behavior, and death from overdose. Much of this comes down to the presence of synthetic opioids and fentanyl analogues that are highly potent in microgram doses[7][8].

The chemical structures of the NPSs are rapidly changing which presents major analytical and forensic challenges. Novel emerging compounds are often not identified by traditional toxicological screening approaches, necessitating the development of advanced analytical methods such as gas chromatography–mass spectrometry (GC–MS), liquid chromatography–tandem mass spectrometry (LC–MS/MS), high-resolution mass spectrometry (HRMS) and AI-assisted forensic toxicology platforms. Accelerated international surveillance and regulatory evolution remain essential to tackling the expanding designer drug epidemic[9][10][11][12].

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The aim of this review is to provide a detailed overview of designer drugs, which includes their classification, chemistry, street names, mechanisms of action, toxicological effects, abuse and forensic detection challenges. The review also discusses recent trends and future directions in forensic toxicology and public health surveillance of new psychoactive substances.

II. EVOLUTION AND CLASSIFICATION OF DESIGNER DRUGS

Designer drugs, commonly referred to as novel psychoactive substances (NPSs), are synthetic compounds intentionally developed to mimic the pharmacological effects of controlled substances while avoiding legal regulation through continuous structural modification [13]. The rapid expansion of NPSs during the last two decades has created substantial public health, toxicological, and forensic concerns worldwide. These substances are frequently marketed as “legal highs,” “research chemicals,” “herbal incense,” or “bath salts,” often misleading users regarding their potency and toxicity [14].

The emergence of designer drugs is strongly associated with clandestine chemical synthesis and online drug markets. Illicit manufacturers continuously modify chemical structures to bypass legislation and routine toxicological screening methods. Minor alterations in functional groups, alkyl chains, aromatic substitutions, and stereochemistry can produce compounds with significantly altered pharmacological activity and toxicological profiles [13]. Consequently, hundreds of new psychoactive substances have appeared globally, making forensic identification and regulation increasingly difficult [15].

Designer drugs are broadly classified according to their chemical structure and pharmacological properties into synthetic cannabinoids, synthetic cathinones, phenethylamines, synthetic opioids, tryptamines, dissociative agents, and designer benzodiazepines [16]. Each category demonstrates distinct receptor interactions, mechanisms of action, physiological effects, and forensic implications.

A. Synthetic Cannabinoids

Synthetic cannabinoids represent one of the largest and most rapidly evolving groups of designer drugs. These compounds were initially synthesized for cannabinoid receptor research but later emerged as recreational drugs because of their cannabis-like psychoactive effects [15]. Unlike Δ9-tetrahydrocannabinol (THC), which acts as a partial agonist at cannabinoid receptors, many synthetic cannabinoids function as full CB1 receptor agonists, producing considerably greater potency and toxicity [17].

Common synthetic cannabinoids include JWH-018, JWH-073, AB-FUBINACA, XLR-11, and MDMB-4en-PINACA. These substances are often sold under street names such as “Spice,” “K2,” “Black Mamba,” and “Scooby Snax” [18]. Their abuse has been associated with severe adverse effects including tachycardia, hypertension, seizures, acute kidney injury, hallucinations, paranoia, psychosis, and sudden death [15], [17].

B. Synthetic Cathinones

Synthetic cathinones are β-keto analogs of amphetamine structurally derived from cathinone, the active psychoactive component of the khat plant (*Catha edulis*) [19]. These compounds act primarily by increasing extracellular concentrations of dopamine, serotonin, and norepinephrine through transporter inhibition or substrate release mechanisms [20].

Common synthetic cathinones include mephedrone, methylone, α-pyrrolidinovalerophenone (α-PVP), and methylenedioxypyrovalerone (MDPV). They are commonly marketed as “bath salts,” “plant food,” or “research chemicals” under street names such as “Flakka,” “Cloud Nine,” and “Meow Meow” [20]. Synthetic cathinones are associated with agitation, hyperthermia, cardiovascular toxicity, hallucinations, aggressive behavior, excited delirium syndrome, and fatal overdose [21].

C. Phenethylamines and NBOMe Compounds

Phenethylamines are structurally related to amphetamine and include stimulant, empathogenic, and hallucinogenic compounds [22]. Structural modifications involving methoxy, halogen, and benzyl substitutions have resulted in highly potent derivatives such as NBOMe compounds. These substances act primarily as agonists of serotonin 5-HT2A receptors and possess significantly greater potency than many classical hallucinogens [23].

Compounds such as 25I-NBOMe and 25B-NBOMe are frequently misrepresented as LSD because of their hallucinogenic properties. However, NBOMe compounds exhibit substantially higher toxicity and have been associated with severe agitation, hyperthermia, seizures, serotonin syndrome, and multiple fatalities [23].

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D. Synthetic Opioids and Fentanyl Analogs

Synthetic opioids have become a major contributor to the global overdose epidemic due to their extreme potency and widespread illicit distribution [24]. Fentanyl analogs including carfentanil, acetylfentanyl, and furanylfentanyl possess exceptionally high affinity toward μ-opioid receptors, resulting in profound respiratory depression and fatal overdose even at microgram doses [25].

Recently emerging nitazene opioids such as isotonitazene and protonitazene have raised serious forensic and toxicological concerns because of their potency exceeding that of fentanyl [25]. These substances are frequently encountered in counterfeit pharmaceutical tablets and adulterated heroin supplies, significantly increasing overdose mortality worldwide.

E. Tryptamines and Dissociative Designer Drugs

Tryptamines are serotonin-related hallucinogenic compounds including AMT, 5-MeO-DIPT, and DMT analogs [26]. These substances produce altered sensory perception, hallucinations, dissociation, and mood disturbances through serotonergic receptor interactions.

Dissociative designer drugs such as methoxetamine (MXE), ketamine analogs, and phencyclidine derivatives primarily act as N-methyl-D-aspartate (NMDA) receptor antagonists [27]. Their abuse has been associated with psychosis, neurotoxicity, cognitive impairment, violent behavior, respiratory depression, and accidental fatalities.

III. CHEMISTRY AND STRUCTURAL MODIFICATIONS OF DESIGNER DRUGS

The rapid emergence of designer drugs is primarily driven by continuous chemical modification of existing controlled substances to produce structurally novel compounds with similar psychoactive effects [28]. Small alterations in molecular structure can significantly affect receptor affinity, lipophilicity, metabolism, potency, duration of action, and toxicological properties. These modifications are frequently designed to evade legal control and avoid detection by conventional forensic screening methods [13].

Structural modification strategies commonly employed in designer drug synthesis include alkyl chain elongation, halogen substitution, esterification, ring substitution, fluorination, and bioisosteric replacement [29]. Such modifications often increase blood–brain barrier penetration and enhance pharmacological activity. Consequently, many novel psychoactive substances demonstrate substantially higher potency and toxicity compared to their parent compounds.

Synthetic cannabinoids represent one of the most structurally diverse categories of designer drugs. Early synthetic cannabinoids such as JWH-018, CP-47,497, and HU-210 were initially synthesized for cannabinoid receptor research [15]. Later generations of synthetic cannabinoids including AB-FUBINACA, ADB-PINACA, 5F-MDMB-PICA, and MDMB-4en-PINACA were produced through structural modifications involving fluorination, indazole ring incorporation, and amino acid ester substitutions [30]. These changes significantly increase CB1 receptor binding affinity, producing severe toxicity and unpredictable psychoactive effects.

Synthetic cathinones are structurally derived from cathinone through β-keto substitution of amphetamine analogs [19]. Further modifications involving aromatic ring substitutions, pyrrolidine ring incorporation, and alkyl side-chain elongation have generated compounds such as α-PVP, MDPV, pentedrone, and eutylone [31]. Pyrrolidine-containing cathinones exhibit particularly strong stimulant effects because of enhanced dopamine transporter inhibition and increased lipophilicity.

Phenethylamines and NBOMe compounds are produced through substitutions on the phenethylamine backbone involving methoxy groups, halogens, and N-benzyl derivatives [23]. NBOMe compounds such as 25I-NBOMe and 25B-NBOMe possess extremely high affinity toward serotonin 5-HT2A receptors, producing potent hallucinogenic effects even at microgram concentrations [32]. Structural modifications greatly influence receptor selectivity and toxicological behavior.

Synthetic opioids demonstrate how minimal structural changes can dramatically increase opioid potency [24]. Fentanyl analogs are generated through substitutions on the piperidine ring, aniline moiety, or N-acyl groups [25]. Carfentanil, for example, contains structural modifications that make it approximately 10,000 times more potent than morphine and nearly 100 times more potent than fentanyl [33]. Newly emerging nitazene opioids exhibit similarly extreme potency and are increasingly implicated in fatal overdoses worldwide.

Designer benzodiazepines such as etizolam, flualprazolam, clonazolam, and diclazepam are synthesized through modifications of classical benzodiazepine structures [34]. Many of these compounds exhibit prolonged half-lives, high receptor affinity, and enhanced sedative effects, increasing the risk of respiratory depression and polysubstance overdose.

The continuous structural diversification of designer drugs presents major challenges for forensic toxicology laboratories. Conventional immunoassays frequently fail to identify newly synthesized analogs because antibodies are optimized for older compounds [35].

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Therefore, advanced analytical techniques such as gas chromatography–mass spectrometry (GC–MS), liquid chromatography–tandem mass spectrometry (LC–MS/MS), high-resolution mass spectrometry (HRMS), nuclear magnetic resonance spectroscopy (NMR), and infrared spectroscopy are essential for accurate characterization and identification of emerging psychoactive substances [36].

The dynamic chemistry of designer drugs highlights the importance of international forensic monitoring systems, toxicological databases, predictive computational models, and rapid analytical method development to address the continuously evolving NPS market.

IV. PHYSIOLOGICAL AND PSYCHOLOGICAL EFFECTS OF DESIGNER DRUGS

Designer drugs produce a wide range of severe physiological and psychological effects because of their strong interactions with neurotransmitter systems including dopaminergic, serotonergic, cannabinoid, glutamatergic, and opioid pathways [37]. The continuously evolving chemistry and high potency of novel psychoactive substances contribute significantly to their unpredictable toxicity and increased risk of fatal intoxication.

Synthetic cannabinoids act as potent agonists of cannabinoid CB1 receptors and are frequently associated with tachycardia, hypertension, seizures, acute kidney injury, respiratory depression, hyperthermia, and sudden cardiac death [38]. Several studies have also reported severe nephrotoxicity and hepatotoxicity following synthetic cannabinoid abuse [39]. Unlike natural cannabis, many synthetic cannabinoids exhibit significantly greater receptor affinity, producing intense toxic effects even at low concentrations.

Synthetic cathinones such as mephedrone, MDPV, and α-PVP stimulate the release and inhibit the reuptake of dopamine, serotonin, and norepinephrine [40]. Their abuse commonly results in cardiovascular complications including arrhythmias, myocardial infarction, hyperthermia, rhabdomyolysis, and multiorgan failure [41]. Synthetic opioids including fentanyl analogs and nitazenes produce profound respiratory depression, unconsciousness, coma, and fatal overdose because of their extremely high potency at μ-opioid receptors [42].

Designer drugs are also strongly associated with severe psychiatric and behavioral disturbances. Common psychological manifestations include anxiety, paranoia, hallucinations, panic attacks, psychosis, agitation, insomnia, aggression, and suicidal behavior [43]. Synthetic cannabinoids are particularly linked with acute psychotic episodes and violent behavior because of their potent CB1 receptor activation [44]. NBOMe compounds and hallucinogenic phenethylamines produce intense hallucinations, altered sensory perception, delirium, and serotonin syndrome [45].

Long-term abuse of designer drugs may result in persistent neuropsychiatric complications including depression, cognitive impairment, emotional instability, addiction, dependence, and chronic psychotic disorders [46]. Repeated exposure to certain synthetic cannabinoids and stimulatory cathinones has additionally been associated with irreversible neuronal injury and long-term alterations in neurotransmitter systems [47].

The increasing abuse of designer drugs demonstrates that these substances are not safe alternatives to traditional illicit drugs but rather highly dangerous synthetic compounds with unpredictable pharmacological and toxicological profiles. Their severe physiological and psychological effects continue to pose substantial challenges for forensic toxicologists, clinicians, law enforcement agencies, and public health systems worldwide.

V. CONCLUSION

Designer drugs and novel psychoactive substances represent one of the most rapidly evolving threats in modern forensic toxicology and public health. Continuous structural modification of these compounds has resulted in highly potent psychoactive substances capable of producing severe physiological toxicity, psychiatric complications, addiction, and fatal overdose. Synthetic cannabinoids, synthetic cathinones, fentanyl analogs, NBOMe compounds, and emerging synthetic opioids have demonstrated toxicological effects that frequently exceed those associated with conventional illicit drugs.

The increasing global abuse of designer drugs, particularly among adolescents and young adults, highlights the urgent need for improved public awareness, toxicological surveillance, forensic monitoring, and international regulatory cooperation. The unpredictable chemistry and pharmacology of these compounds significantly complicate clinical management and forensic investigation because newly emerging analogs often remain poorly characterized.

Overall, designer drugs are not harmless or safer alternatives to conventional narcotics. Instead, they represent highly dangerous synthetic substances with serious physiological and psychological consequences that can lead to irreversible organ damage, severe psychiatric disorders, and death.

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Continued multidisciplinary collaboration among forensic scientists, toxicologists, healthcare professionals, policymakers, and public health agencies is essential to effectively address the growing global crisis associated with designer drug abuse.

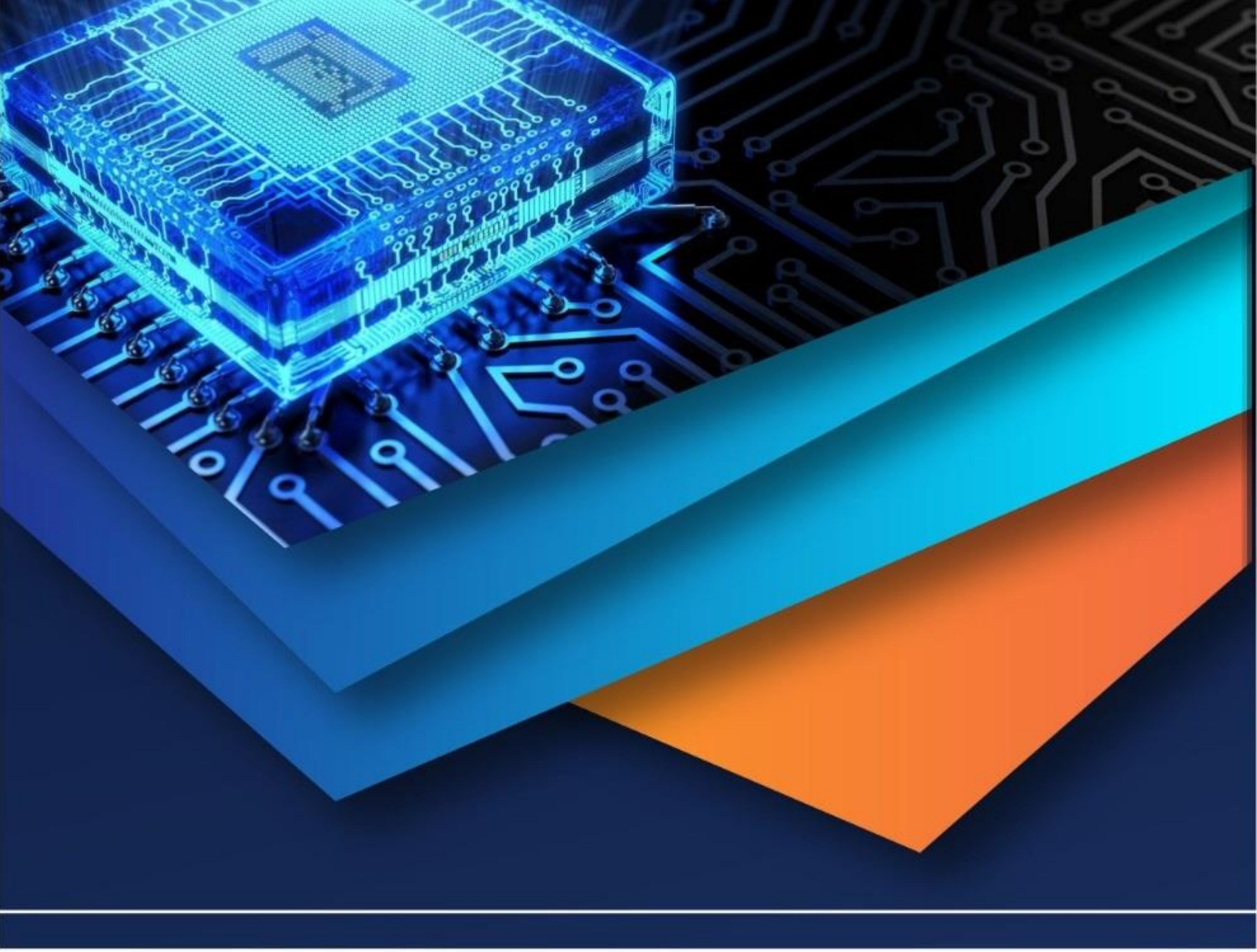
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