

Chemistry, Pharmacology and Toxicology of New Designer Drugs - A Comprehensive Review

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Abstract

Drugs have been used for recreational purposes since time immemorial. Addicting potential and the propensity to harm has led to a ban on many of these drugs. New compounds are being developed to circumvent the ban. They are similar in effect to the banned drugs but are slightly different in their chemical structure so that they can escape detection in the standard drug tests. These drugs are commonly known as designer drugs or new psychoactive substances (NPS). This work aimed to do a comprehensive review on chemistry, pharmacology and toxicology of new designer drugs for establishing the basic knowledge about them, focusing on their assessment and management and recent methods for their detection. According to the United Nations Office on Drugs and Crime (UNODC) classification, NPS include the following groups: Synthetic cannabinoids, synthetic cathinones, piperazine, phenethylamines, ketamine analogues, plant-based substances (Kratom, *Salvia Divinorum*) and miscellaneous substances (aminoindanes and tryptamines). NPS have become a global phenomenon with over 100 countries and territories from all regions of the world having reported one or more NPS. Up to December 2015, more than 600 substances have been reported to the UNODC Early Warning Advisory (EWA) on NPS by Governments, laboratories and partner organizations. NPS represent a challenge both in forensic analytical toxicology as well as in clinical toxicology as they may cause serious toxicity and can escape detection in the standard drug tests. Clinicians should keep designer drugs in mind when evaluating substance use in young adults or in anyone presenting with acute neuropsychiatric complaints. Coordination among emergency medical personnel, forensic toxicologists, scientific researchers, law enforcement and policymakers is essential to foster more effective responses in dealing with this evolving drug-abuse phenomenon.

Keywords: *Designer drugs, New Psychoactive Substances and Legal high.*

Introduction

The term 'designer drugs' had been traditionally used to identify synthetic substances but has recently been broadened to include other psychoactive substances that mimic the effects of illicit drugs. They are produced by introducing slight modifications to the chemical structure of controlled substances to circumvent drug controls (UNODC, 2013a).

The majority of new recreational designer drugs can be described by their effects as hallucinogenic, stimulant, opioid-like and they may have a combination of these effects. New designer drugs as compared to traditional drugs of abuse are cheap, easy to obtain and not detectable by standard toxicology screens. They are generally marked with disingenuous labels such as "not for human

consumption", "herbal incense", "Spice" and "bath salts" to avoid drug control measures (Spaderna et al., 2013). Designer drugs have many concepts as research chemicals, legal highs, synthetic legal intoxicating drugs, novel psychoactive substances and NPS. The concept of "NPS" is the latest concept. The use of the term "new" does not refer to the time when a substance was first identified or synthesized, but to when it emerged in the global market for recreational use (UNODC, 2013a and UNODC, 2013b).

Aim of the work

As a result of increasing the number of designer drugs on the market, a comprehensive review on its chemistry, pharmacology and toxicology is required for

1. Introducing and establishing the basic knowledge about these new designer drugs for further researches
2. Focusing on their assessment and management
3. Exploring recent advances in analytical toxicology methods for their detection.

Historical background of designer drugs

Until the last third of the 20th century, drugs were either wholly natural (e.g., marijuana) or were processed products that had their origins in natural substances. For example, cocaine was produced from the coca plant, heroin from opium poppies and wine from fermented grapes. (Carpenter, 2015). The Controlled Substances Act of 1970 established a framework for regulating substances of abuse within the United States by scheduling them based upon medical use, abuse liability and risk of developing physical or psychological dependence. Following passage of the Controlled Substances Act of 1970, a

number of compounds were abused to mimic the effects of popular illicit drugs while avoiding regulation by making modifications to the chemical structure of the controlled substances. The term 'designer drug' was coined in the early 1980s to describe such compounds. Synthetic opioids as 'China White' were the first compounds termed designer drugs and produced by fentanyl modification to mimic the effects of heroin (Ziporyn, 1986). Marketers of designer drugs began to sell these drugs over the internet in the late 1990s and early 2000s under the term of "research chemicals" and labeled "not for human consumption" to circumvent drug abuse legislation (Camí and Farre', 2003).

Origin of designer drugs

Many designer drugs begin as legitimate pharmaceuticals or medicines, created as part of drug manufacturers, research and experimentation. Throughout the drug discovery process, information published by pharmaceutical companies and research institutions is used by clandestine chemists to manufacture and market endless variety of designer drugs. Other designer drugs started as botanicals. Designer drug chemists reformulate these chemicals found in nature to produce "legal" products with increased potency (Paul, 2014).

Categories of New Psychoactive Substances

NPS can be classified by their chemical structure, psychoactive properties and by their source (plant,

synthetic or combined). NPS groups include,

1. Synthetic cannabinoids (SCs)
2. synthetic cathinones
3. Piperazine derived designer drugs
4. phenethylamines
5. ketamine analogues
6. plant-based substances as Kratom and Salvia Divinorum
7. Miscellaneous substances
asaminoindanesand tryptamines
(UNODC, 2013 b).

The UNODC questionnaire on NPS received more than **240** responses from **80** countries and territories, indicating a high level of interest. All NPS groups have emerged in all regions, except Africa where, so far, no synthetic cathinones and phenethylamines have been reported (Fig. 1). Egypt reported the emergence of plant-based substances (Salvia divinorum), SCs, ketamine and piperazines (BZP)(UNODC, 2013b).

Global emergence of New Psychoactive Substances

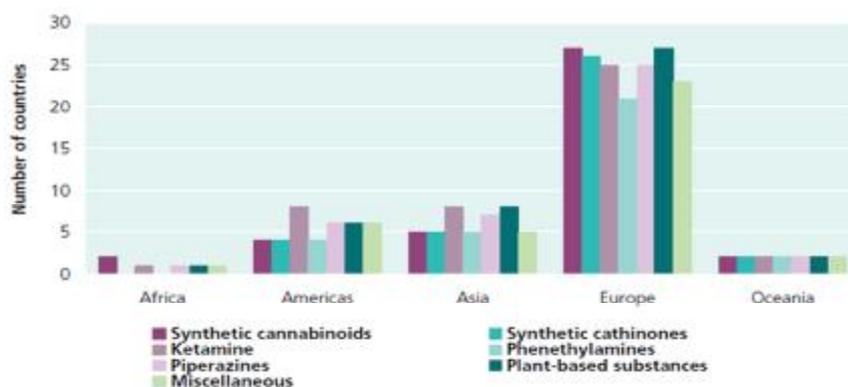


Figure (1): Regional emergence of NPS by groups (UNODC, 2013b).

The majority of NPS in the number of reports worldwide to UNODC between **2008** and **2013** were SCs and synthetic cathinones followed by Phenethylamines (UNODC, 2014). Up to December **2015**, more than **600** substances have been reported to the UNODC Early Warning Advisory (EWA) on NPS (UNODC, 2015). NPS production is geographically unlimited as all areas of the world participate with increasing frequency. The Internet plays an important role in the NPS business, as it provides information on their synthesis, extraction, identification and substance use (Karila et al., 2015).

Synthetic cannabinoids:

SCs are group of compounds with a wide range of chemical structures, have been developed by scientists with the hope of achieving selectivity toward one or the other of the cannabinoid receptors (CBRs) CB1 and CB2. SC products first emerged in Europe in **2004** as “Spice”. Today, SC products are distributed worldwide under countless names, such as “K2,” “Black Mamba,” “Cloud 9,” and “Voodoo”(Fig. 2) (Spaderna et al., 2013).



Figure (2):the colorful packages of the SCs (Spaderna et al., 2013).

Spice Products produced by dissolving SCs in an organic solvent, acetone or alcohol. The solution is then sprayed onto dried plant material and the final product is packed and sold after drying(Presley et al., 2013). Egypt reported first emergence of SCs in **2010**. Only a few SCs are structurally related to Delta-9-THC and the others belonging to different and various chemical families(Fig,3). SCs can be divided based upon their chemical structure into, Classical cannabinoids e.g., HU-210, Nonclassical cannabinoids e.g., CP-55,940, Hybrid cannabinoids e.g., AM-4030, Aminoalkylindoles e.g., JWH-015, Eicosanoids and Others e.g., APINACA ((UNODC, 2013a and Salomone, 2015).

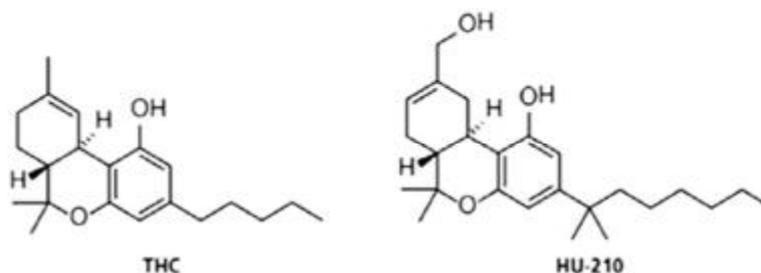


Figure (3): structure similarity of THC and HU-210(Salomone, 2015).

SCs exert their effects by binding to CB1 and CB2 receptors like THC. CBRs are G-protein coupled receptors for which activation results in presynaptic hyperpolarization through changes in calcium influx and potassium efflux, resulting in neuronal hyperpolarization and a decrease in neurotransmitter release. They are used by oral and inhalational routes. Clinical case reports of intoxicated patients with SCs describe a variety of somatic and neuropsychiatric effects. The most prevalent side effects include tachycardia, hypertension, hyperthermia, tremors, ataxia, agitation, paranoia, delusions, anxiety, vomiting, conjunctival injection, rhabdomyolysis and acute renal failure. Case reports of Spice tolerance, withdrawal and drug dependence have described(Gurney et al., 2014).

Synthetic cathinones:

Synthetic cathinones are synthetic derivatives of the natural cathinone, one of the psychoactive compounds present in *Catha edulis* (khat) plant. They are emerged in the recreational drug markets as legal alternatives to amphetamine, 'ecstasy' or cocaine and sold as 'bath salts' or 'plant food'. Bath salts are sold under several inexplicit brand names, including Bloom, Ivory Wave, Purple Wave, and Vanilla Sky (Valente et al., 2014). Multiple deaths reported in by international media and the medical literature have been linked to bath salt products indicating the urgent need to raise awareness and educate the public and medical communities on this topic (Rosenbaum et al., 2012).

They are closely related to amphetamines, the difference being the ketone group introduced at the β -position of the amino alkyl chain attached to the phenyl ring so, they are called β -keto-amphetamines (Fig.4). There are at least 12 different types of synthetic cathinones, with mephedrone, methylon and methylenedioxypropylamphetamine (MDPV) being the most commonly used by the purchasers (Baumann et al., 2014 and Valente et al., 2014).

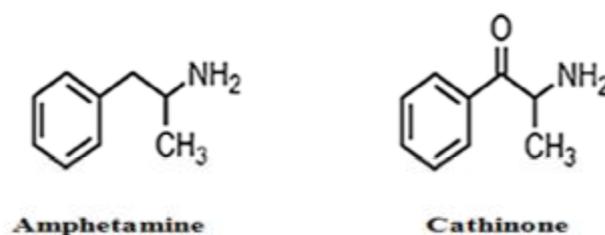


Figure (4): Structure similarity of cathinone to amphetamine (Baumann et al., 2014).

Synthetic cathinones are usually acquired as crystalline powder, with white or brownish coloration that can occasionally be presented as capsules or tablets. They can be used by multiple routes of exposure, with the nasal insufflation and oral ingestion being the most common. Inhalation, gingival and sublingual delivery, intravenous injection, and rectal administration of synthetic cathinones products have also been reported. The stimulatory effects of synthetic cathinones are induced by elevations in synaptic catecholamine concentrations. They have received large popularity, particularly among young people, for their cocaine and amphetamines like psychoactive and sympathomimetic effects (Valente et al., 2014 and Coppola and Mondola, 2012). The toxic effects of synthetic cathinones are mainly due to their enhancement of the sympathetic nervous system activity. Users of 'bath salts' report a number of negative physical and psychiatric effects. The most common manifestations of acute toxicity include tachycardia, hypertension, hyperthermia, seizures, mydriasis, paranoid psychosis, depression, abdominal pain and vomiting. Some users developed severe complications as rhabdomyolysis, kidney damage, hyponatremia, hypoglycemia and Serotonin syndrome (karilia et al., 2015). Data currently available have shown that the frequent consumption of synthetic cathinones induces tolerance, dependence, craving and withdrawal syndrome after sudden suspension (Coppola and Mondola, 2012).

Piperazine derived designer drugs:

The basic molecule of this group is piperazine that was first introduced in medicine in **1953**, for its anthelmintic properties. Piperazine derivatives (PZDs) have emerged as a new group of recreational drugs over the last decade. They are sought to be used for their amphetamine like effects (**Arbo et al., 2012**)

Chemically, the backbone of PZDs is the piperazine moiety attached to an aromatic group (**Fig.5**). They are divided into two classes, benzyl-piperazines as BZP (**1-benzylpiperazine**) and phenyl-piperazines as mCPP (**1-(3-chlorophenyl) piperazine**) and MeOPP (**1-(4-methoxyphenyl)piperazine**) (**Arbo et al., 2012**).

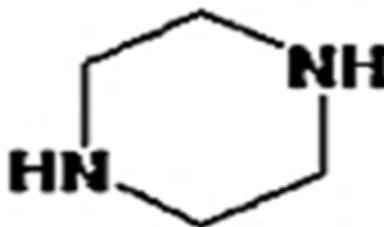


Figure (5): Chemical structure of Piperazine(**Arbo et al., 2012**)

PZDs are sold as ecstasy pills, party pills and consumed as capsules and tablets. The reported side effects of PZDs are tachycardia, hypertension, chest pain, agitation, anxiety, headache, tremor, mydriasis, insomnia, urine retention, nausea, vomiting and abdominal pain. More severe toxicity may include seizures, collapse, hyperthermia, extrapyramidal features and respiratory failure (**Schep et al., 2011**).

Phenethylamines:

This group of designer drugs includes large number of compounds as amphetamine and methamphetamine. **2, 5-Dimethoxy phenethylamines (2-C drugs)** and Paramethoxymethamphetamine (PMMA) are the most recently used phenethylamines. **2-C** drugs are group of newly substituted designer hallucinogens. The most recent **2C** drugs to become popular are **2C-I** and **2C-I-NBOMe**. they are available in tablets, capsule, powder and liquid formulations. The majority of patients suffering from **2C** toxicity exhibit a combination of sympathomimetic syndrome, serotonin syndrome and

hallucinations (**Dean et al., 2013 and UNODC, 2013b**).

PMMA is similar in structure to **3,4-methylenedioxymethamphetamine "MDMA"** but substantially more toxic. Users of PMMA report that they experienced euphoria, psychedelic effects and increased energy. Side effects of PMMA include hyperthermia, agitation, rhabdomyolysis, hallucination, arrhythmia, convulsions, sweating, headache, difficulty speaking, serotonin syndrome, coma and death (**Páleníček et al., 2011**).

Ketamine analogues:

Ketamine is a well-known anesthetic, its potent hallucinogenic and dissociate effects have afforded ketamine as a recreational drug used. Recently, the most common synthetic analogue of ketamine is methoxetamine. Methoxetamine is an odorless white or offwhite powder. Its street names are "M-ket" and "Special K". Severe side effects as paranoia, anxiety, respiratory depression, tachycardia, nystagmus, laryngospasm and pulmonary edema have been reported in users (**Rosenbaum et al., 2012 and UNODC, 2013a**).

Plant-based substances:

• ***Salvia divinorum***

Salvia divinorum is a naturally occurring herb that has been used in Mexico for centuries. It is administered via chewing or smoking routes. Its desired effects include a state of “trance” that is similar to that produced by ketamine and cannabis. Effects of *salvia* intoxication include anxiety, dysphoria, confusion, language impairments and fear associated with “bad trips”. Cases of addiction have been reported but its prevalence has not been studied (Rosenbaum et al., 2012 and UNODC, 2013a).

• ***Kratom (Mitragynaspeciosa)***

Kratom is a tree found in tropical and subtropical regions of South East Asia. The fresh leaves are chewed while the powder form is brewed into tea. It has opium-like effect. It was also used as a in traditional medicine for common illnesses such as coughing, diarrhea, muscle pain and to cure morphine addicts as it is effective in relieving opiate withdrawal symptoms. However, its use as a NPS in the global market has been recently reported Heavy use can lead to adverse effects as seizures, profound sedation, nausea, vomiting and tremors (UNODC, 2013a).

Miscellaneous substances:

Miscellaneous group of NPS is not commonly used and include aminoindanes and tryptamines. Aminoindanes have been sold as NPS for their ability to produce effects similar to MDMA. They are commonly found in powder form and crystals. The use of tryptamines increased over the past five years. Synthetic tryptamines as alpha-methyltryptamine (AMT) produce hallucinogenic effects in humans due to the structural similarities between these tryptamines and some naturally occurring hallucinogenic tryptamines as psilocybin and psilocin.

Tryptamines users exhibit vital signs abnormalities as, tachypnea, hypertension and hyperthermia. Reports of trismus, anxiety, diarrhea, nausea, vomiting, diaphoresis, palpitations, mydriasis rhabdomyolysis and renal failure are also described (UNODC, 2013a and Jovel et al., 2014).

Management of new designer drugs toxicity

NPS present a new challenge to acute care physicians. No specific antidotes are available for their toxicity and activated charcoal is not useful unless there has been significant oral ingestion. Most non psychiatric symptoms are self-limited and resolve within one to several days with supportive treatment. Unpleasant psychological effects of acute intoxication, as anxiety, agitation and paranoia can be managed with supportive treatment (Weaver et al., 2015).

Detection of new designer drugs

Analysis of new designer drugs is a major problem as it takes some time to add brand new substances in mass spectra libraries in order to make them detectable in routine screenings. Specific immunoassays for new designer drugs do not exist and cross-reactivities with common routine assays have not been investigated systematically, they are known for only very few compounds. The most commonly used methods for analysis of these substances in biological samples as plasma, blood and urine are Gas Chromatography/Mass Spectrometry (GC-MS/MS) and Liquid Chromatography Tandem Mass Spectroscopy (LC-MS/MS) after sample preparation with liquid-liquid extraction or solid-phase extraction (Namera et al., 2015).

Summary and Conclusion

Novel or new psychoactive substances are newly used designer drugs. They are analogues or chemical derivatives of controlled substances designed to produce effects and health risks similar to the controlled substances they mimic. The continuous emergence of NPS poses constant challenges for both clinical and forensic toxicologists. They pose obvious risks because there is no quality control in their production, their pharmacological effects are poorly understood and clinical data are limited to cases from emergency room admissions. The effects of NPS are often much more potent than the illicit drugs which they are intended to mimic. Most NPS are not detected by routine toxicology screens. Clinicians should keep designer drugs in mind when evaluating substance use in young adults or in anyone presenting with acute neuropsychiatric complaints. Treatment of acute intoxication involves supportive care targeting manifesting signs and symptoms. Long-term treatment of designer drug use disorder can be challenging and is complicated by a lack of evidence to guide treatment. Young persons who present to emergency room admissions with agitation and cardiovascular and/or psychiatric manifestations of unclear origin and whose drug screening tests are negative may be suffering from intoxication with a NPS.

Recommendations

- More basic research in animal models is needed to understand the accurate pharmacology of NPS and to evaluate the consequences of their acute and chronic exposure.
- There is a need for evidence-based-treatment recommendations for acute intoxications. New strategies to

analyze these compounds in clinical and forensic cases are needed.

- Education of physicians in emergency room and general hospitals about classes of NPS and their most common side effects.
- Measures against the role of internet in distribution of NPS must be taken.
- Newly developed analytical methods for detecting NPS must be made widely available to assist in identifying novel substances as they emerge in the recreational drug market rapidly.
- Controlling the influx of NPS from overseas laboratories is a complex political and economic issue which will need international cooperation.

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