

*“ New designer drugs: An emergent community challenge”*

Authors

Basma Abd El-aal<sup>1</sup> Mohamed shaban Hemeda<sup>1</sup> Heba Youssef Sayed<sup>1</sup>

Forensic Medicine and Clinical Toxicology, Faculty of Medicine, Port Said University

**ABSTRACT:**

The availability of drugs with psychotropic effects on worldwide market constitutes a significant threat to public health and a problem for drug policy. Frequently, little is known about the detrimental effects on health and the social implications, making prevention and therapy difficult. It is difficult to analyze and identify a significant number of chemically varied drugs prevalent in pharmaceuticals marketplaces at the same manner. To respond to this circumstance, it is necessary to monitor, share information, provide early warning, and be aware of risks. NPS has been referred to in the market as "bath salts," "legal highs," and "research chemicals." According to the United Nations Office on Drugs and Crime," abusive substance, whether in its original form or a mixture, that is not controlled by the 1961 International Convention on Illicit Drugs or the 1971 Convention on the Control of Psychotropic Drugs but which may pose a global health threat is referred to as a "new psychoactive substance" NPS. Numerous NPS were initially synthesized decades ago, therefore the descriptor "new" does not always indicate to new items .instead, it refers to compounds that have recently become accessible to consumers.

**Keywords:** New psychoactive substances, Legal highs, Synthetic cathinones, Synthetic cannabinoids, Toxicity.

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[vice\\_dean\\_postgraduate@med.psu.edu.eg](mailto:vice_dean_postgraduate@med.psu.edu.eg)

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## Introduction

By altering the chemical composition of other psychoactive compounds, synthetic or "designer" drugs can be created that are structurally related to yet distinct from illegal psychoactive narcotics. Designer drugs, which emerged in the 1960s as a means of getting around the country's drug laws, have become a growing trend in the last few decades. These illegal substances are disguised in packaging under names like "research chemicals," "incense," "bath salts," or "plant food," among others, and may have warnings like "not for human usage" or "not for use to teenagers." The vast majority of modern designer medications have hallucinogenic, stimulant, or opioid-like effects. <sup>(1)</sup>

Research chemicals, legal highs, synthetic legal intoxicating substance, novel psychoactive substances are some of the different classifications for designer drugs. The most current is the "NPS". The term "new" refers to the time that a substance first entered the international market for recreational purposes, not to its discovery or production. <sup>(2)</sup>

Standard drug testing could miss both established substances and newly discovered ones, and details on the accompanying negative consequences are typically unavailable. Recognizing the principles of action and potential therapeutic consequences of designer medications is crucial for healthcare professionals who manage people who are drunk. <sup>(3)</sup>

Figure (1) New psychoactive substances <sup>(14)</sup>



## New Psychoactive Substance Categories

NPS are categorized by their chemical structure, psychoactive characteristics, and source (plant, synthetic, or mixed).

1. Synthetic cannabinoids (K<sub>2</sub>, spice)
2. Synthetic cathinones (Bath salts)
3. Designer drugs made from piperazine
4. Phenethylamines
5. Analogues of ketamine
5. Kratom and Salvia Divinorum: examples of plant-based substances.
7. Other chemicals such as Aminoindanes and Tryptamines <sup>(2)</sup>

## Synthetic cathinones



Figure (2) Bath salts <sup>(18)</sup>

In recent years, synthetic cathinones have been widely used as illicit substances. media coverage in addition to the Internet's general availability have contributed to their quick increase. They are often marketed as "bath salts" or "plant food" and stamped "not suited to human usage" in order to circumvent regulations against drug abuse. Cathinone, a naturally existing beta-ketone amphetamine substitute, is found in the leafy parts of the *Catha edulis* plant. <sup>(4)</sup>

Several brand names, such as Bloom, Ivory Wave, Purple Wave, and Vanilla Sky, are used to market bath salts. Synthetic cathinones' poisonous effects are mostly brought by an increase in sympathetic nervous system activity. Bath salt users describe a variety of harmful physical and psychological impacts.

The most common symptoms of acute poisoning are tachycardia, elevated blood pressure, high temperatures, epileptic fits, mydriasis, paranoid psychosis, depressive disorders, discomfort in the abdomen, and vomiting. Serious adverse consequences such serotonin syndrome, rhabdomyolysis, kidney failure, state of hyponatremia and hypoglycemia were experienced by some users. According to data now available, frequent use of synthetic cathinones results in tolerance, dependency, yearning, and withdrawal syndrome after abrupt cessation. <sup>(2)</sup>

## Synthetic cannabinoids (SCs)

Scientists have created a class of compounds known as Synthetic cannabinoids (SCs) with a range of chemical structures in the hopes of achieving selectivity for either the CB1 or CB2 receptors for cannabis. SC items first debuted as "Spice" in Europe in 2004. Current trademarks for SC items sold worldwide include "K<sub>2</sub>," "Black Mamba," "Cloud 9," and "Voodoo." <sup>(2)</sup>

Spraying dried plant material with synthetic cannabinoids that have been dissolved in a solvent is done. Once the solvent has vanished and the plant material has once again dried, the final item can be crushed and packed. Although powder has occasionally been offered, a loose leaf or pre-rolled spice is the most prevalent form of marketing. It is frequently smoked using cigarette papers, a liquid pipe, or a regular cannabis pipe. Spice has been flavored with a variety of components, which helps to explain why certain Spice products are marketed as potpourri. Additionally, some flavors may be linked to specific synthetic cannabinoids and plant-based substances. <sup>(5)</sup>



Spice <sup>(15)</sup>/

Figure (3) K2

Like Tetrahydrocannabinol, SCs function by binding to both CB1 and CB2 receptors. CBRs are G protein coupled receptors that alter the inflow of calcium and potassium outflow to generate presynaptic hyperpolarization, which in turn causes neuronal hyperpolarization and a reduction in the release of neurotransmitters. They are inhaled and taken orally. A wide variety of mental and physical manifestations are described in clinical case reports of intoxicated SCs people. The most frequent adverse reactions are tachycardia, high blood pressure, high temperatures, tremors, ataxia, agitation, psychosis, delusions, anxiety, vomiting, conjunctival injection, rhabdomyolysis, and acute renal failure. There have been reports of cases of spice dependency, withdrawal symptoms, and tolerance. <sup>(2)</sup>

## Piperazine derivatives designer drugs

Piperazine derivatives are chemical substances that are produced in labs and sold mainly as "dietary supplements" or "legal highs." The main compounds include Benzylpiperazine (BZP), Trifluoromethylphenylpiperazine (TFMPP), Metachlorophenylpiperazine (mCPP), 1-(4-Methoxyphenyl)piperazine (4-MeOPP), and Methylenedioxybenzylpiperazine (MDBP). By enhancing dopaminergic, noradrenergic, and mostly serotonergic neurotransmission as well this class of NPS exerts stimulant properties. Sleeplessness, headaches, nausea, agitation, melancholy, paranoia, and auditory hallucinations are some of the signs of poisoning. <sup>(6)</sup>

An electrocardiogram and sodium level in the plasma estimation should be done on individuals who have piperazine designer drug poisoning when they visit a hospital. For patients with moderate to severe toxicities, benzodiazepines, intravenous fluids, and antiemetics may be necessary, the presentation of these persons should be watched for 6 to 8 hours after ingestion in case of late seizures. Seizures should be managed with airway control and benzodiazepines. Status epilepticus may require the use of barbiturates as a therapy. Antipsychotics are rarely advised as the first line of treatment for agitation. Because it can impair temperature regulation, result in extrapyramidal negative consequences such as dystonic responses, or result in abnormal heart rhythms or low blood pressure, care is crucial. If control of blood pressure is necessary, sodium nitroprusside, nitroglycerin, isosorbide dinitrate, or  $\alpha$ -adrenergic blockers should be administered intravenously until the elevated blood pressure is controlled. Additionally, clonidine has been effectively utilized to lower blood pressure in a BZP overdose patient. <sup>(6)</sup>

## Phenethylamine

Amphetamine and methamphetamine are just two examples of the diverse compounds found in this group of designer medications. The latest types of phenethylamines to be used are paramethoxymethamphetamine (PMMA) and 2,5-Dimethoxy phenethylamines (2-C medications). A class of recently produced designer hallucinogens called 2-C medications. The 2C-I and 2C-I-NBOMe drugs, which come in tablet, pill, powder, and liquid formats, are the most current 2C medications that are gaining popularity. The vast majority of people with 2C poisoning exhibit a mix of hallucinations, serotonin syndrome, sympathomimetic syndrome, and other symptoms. <sup>(2)</sup>

Similar in structure to 3,4-methylenedioxymethamphetamine ("MDMA"), PMMA is much more dangerous. Users of PMMA claim to feel exhilarated, having psychedelic experiences, and having greater energy. PMMA may cause side effects such as high temperatures, agitation, rhabdomyolysis, psychosis, cardiac arrhythmia, epileptic fits, shivering headache, trouble speaking, serotonin syndrome, coma, and death. <sup>(2)</sup>

## Ketamine analogues

Methoxetamine is a form of powder that has no color or smell and is frequently sold in tiny, eye-catching packages. Sometimes it is marketed as "plant food" or "pond cleaner" and may have warnings like "not suited to human use" or "warning for researchers only" that are common on designer drug labels. It indicates that China is where most methoxetamine is made. There are various other names for methoxetamine, including "MXE," "m-ket," "k-max," and "mexxy." It is typically delivered nasally, but it can also be given orally, rectally, intramuscularly (IM), and intravenously (IV). Methoxetamine users express ketamine-like dissociative symptoms, similar to a near-death experience, such as loss of sensation, derealization, visual hallucinations, and dissociation from their bodies. <sup>(7)</sup>



## Plant based substance of abuse

### Salvia divinorum



Figure (4) Salvia Divinorum<sup>(16)</sup>

Teenagers are becoming more and more accustomed to the non-water-soluble psychedelic salvia divinorum. Salvia is an extremely selective complete agonist of monkey and cloned human brain kappa-opioid receptors, despite the fact that its psychotomimetic effects are similar to those of serotonergic agonists and N-methyl-D-aspartate (NMDA) glutamate antagonists. Depersonalization, laughing, telepathy and feeling self-conscious have all been connected to salvia. Following use, these adverse effects disappear in 30 minutes. Although salvia has been outlawed in many countries, it is still allowed and readily available online in some places.<sup>(8)</sup>

### Kratom

Southeast Asian tropical trees grow kratom. Its leaves can produce psychotic symptoms, mental dependence, and sedation when used in high amounts. They also have hypnotic and stimulant qualities. Mitragynine and 7-hydroxymitragynine are the two major psychoactive substances found in kratom leaf. After being crushed, the leaves are either smoked, soaked in tea, or put into gel capsule. The most frequent type of abuse is oral ingestion of a tablet, capsule, or extract. Additionally, kratom leaves can be consumed or processed into a drink. At low doses, it has stimulant impacts causing users to feel more alert, physically active, and chatty. Users get effects of sedation at high doses. Use of kratom can lead to addiction. There have been several recorded cases of psychosis brought on by kratom use, in which kratom addicts had psychotic symptoms such hallucinations, delusion, and confusion. Some of the adverse effects include nausea, itchiness, shivering, thirst, constipation, higher urine production, a rapid heartbeat, vomiting, tiredness, and a reduction in appetite. Kratom users have also mentioned hallucinations, liver damage, hepatic toxic effects, anorexia, and losing weight.<sup>(9)</sup>



Figure (5) Kratom (A) Trees (B) Leaves<sup>(17)</sup>

## **Aminoindanes and Tryptamines**

Aminoindane designer drugs were accessible to consumers after the eventual legalization of first-generation designer stimulants like mephedrone. They are conformationally restricted analogs of amphetamine that were first investigated as bronchodilator, analgesic, and anti-Parkinson medications, and later as drugs with efficacy in psychiatry. These designer medicines have adrenergic, dopaminergic, and serotonergic receptor affinities and are monoamine transporter substrates, just like amphetamines. Designer medications containing aminoindane can have side effects including agitation, nervousness, attacks of panic, headache, sleeplessness, hallucinations, and palpitations. Although the potential for aminoindane serotonergic toxicity in humans has not been investigated, serotonin syndrome symptoms have been observed in rats following an excessive dosage of Methylenedioxy-2-aminoindane (MDAI).<sup>(10)</sup>

Similar to other psychedelics, tryptamine psychedelic substances alter cognition and have the potential to lead to severe mental disorders in users, such as acute psychosis. Designer drugs that contain tryptamine can cause agitation, sense of disorientation, confusion, hallucinations, memory loss, catalepsy, mydriasis, tachypnea, high blood pressure, and palpitations. Consuming 5-Methoxy-N, N-Diisopropyltryptamine (5-MeO-DiPT) has been associated with ongoing delusions and hallucinogen-persisting perceptual problem. In extreme cases, rhabdomyolysis and sudden kidney damage have been caused by the use of tryptamine designer drugs.<sup>(10)</sup>

## **Management of new designer drugs toxicity**

There are no specific antidotes for designer drug toxicity. Unless there has been sufficient oral consumption, activated charcoal is ineffective. With medical support, the majority of nonpsychiatric symptoms are reversible and go away in one to several days. Anxiety, agitation, and delusion are undesirable psychological signs of serious intoxication that can be treated with supportive treatment. Placing the distressed user in a calm environment and sustaining gentle contact is frequently enough to alleviate the acute symptoms.<sup>(13)</sup>

## **Case of synthetic cathinones**

Police discovered a 25-year-old individual moving erratically, behaving violently, and frothing at the lips after injecting bath salts. His ER vitals were alarming, with a rectally high temperature of 41.4 degrees C and pulse of 175 beats per minute. A physical exam revealed mydriasis, an eye deviation to the right, and significant warmth. He grew agitated before being intubated with etomidate and succinylcholine. Within an hour, with the help of the ice packs and cooling coverings, his temperature and pulse were back to baseline. Notable values included the white blood cell count of 17,000/mm<sup>3</sup>, potassium of 5.1 mEq/L, serum bicarbonate of 14 mEq/L, creatinine of 2.87 mg/dL, glucose of 45 mg/dL, troponin of 3.24 ng/mL, and lactate of 7 mg/dL. The results of the urine drug test showed an existence of benzodiazepines, which had been administered 90 minutes before the sample was taken. His ECG, head CT scan, and cerebrospinal fluid all showed no abnormalities. Over the following two days, the patient developed renal failure, fulminant liver failure, dissemination of intravascular coagulation, and rhabdomyolysis. His INR was 9.3, his creatinine kinase level was 253,377 U/L, his creatinine level was 10.2 mg/dL, and his troponin level was 29 ng/ml. His aspartate aminotransferase level peaked at 16,687 U/L. He needed hemodialysis while in the medical intensive care unit (MICU) due to anuric failure of the kidneys, and he had to be intubated for 9 days. By day 13, his mental status was back to normal, and by day 18, all of his test results—with the exception of creatinine—had returned to normal. The patient's creatinine urine from the day of admission was measured using liquid chromatography with high performance after one month of hemodialysis, and it was discovered to contain a level of 3,4

methylenedioxypropylamphetamine (MDPV) of 140 ng/ml. A potent dopamine and norepinephrine transporter inhibitory substance, MDPV is a synthetic compound with structural similarities to pyrovalerone. Pyrovalerone is 9 and 13 times more effective than cocaine at inhibiting the uptake of dopamine and norepinephrine, respectively. Although the precise mechanism behind this 25-year-old man's clinical history is uncertain, it is believed that MDPV produced hyperthermia by way of a central disturbance. The uncoupling impact of MDPV on skeletal muscle proteins and oxidative phosphorylation, as well as increased muscle activity or agitation, are other possible causes of the elevated body temperature. MDPV is nevertheless strongly associated with the emergence of hyperthermia. It is unclear, however, whether the severe agitation and hyperthermia that followed the MDPV exposure or the end organ effects documented in this patient were to blame. However, treatment for MDPV intoxication should be the same as for other sympathomimetic drug intoxications, i.e., intensive supportive care and benzodiazepine control of the patient's agitation. <sup>(11)</sup>

## **Case of synthetic cannabinoids**

A 15-year-old boy was found unresponsive and had been found with a pulse of 172 beating per minute and a blood pressure measurement of 162/57 millimeters of mercury when he got to the emergency room. His oxygen saturation levels and breathing rate on room air were both 99%, or 16 breaths per minute. An EKG taken at the time revealed the existence of sinus tachycardia. When the patient regained consciousness, he or she expressed fatigue and a slight headache but was unable to recall what had happened. He smoked a cigarette with "K<sub>2</sub>" on it for thirty minutes before going into the emergency department. The amount as well as the nature of the item used were both uncertain. Thirty minutes after he arrived, his heart rate and blood pressure were 95 BPM and 129/65 mm Hg, respectively. The reason for the patient's transfer to the PICU was so telemetry could be used to track the patient's heart rate, blood pressure, and arrhythmias. The patient has a long history of abuse of alcohol and marijuana in particular. Before his admission, he claimed not to have taken any further drugs or alcohol, nor had he been taking any prescription or over-the-counter medications. Upon admission to the PICU, tests were done on the patient's serum and urine for acetaminophen, ethanol, and salicylates; all results, including those for cannabis, were negative. His serum chemistry results were normal save for serum potassium of 2.4 mEq/L (normal range 3.5 to 5 mEq/L). The patient was put on continuous monitoring and was maintained with injectable potassium fluid. Overnight, the patient's potassium levels in the serum, heart rate, and blood pressure all returned towards normal. The following morning, when his mental state had returned to normal, he was sent home with outpatient counseling for his substance misuse. <sup>(12)</sup>

## **Conclusion**

Designer drugs have become a growing trend in the last few decades. The vast majority of modern designer medications have hallucinogenic, stimulant, or opioid-like effects. Standard drug testing could miss both established substances and newly discovered ones, and details on the accompanying negative consequences are typically unavailable. Recognizing the principles of action and potential therapeutic consequences of designer medications is crucial for healthcare professionals. There are no specific antidotes for designer drug toxicity. Anxiety, agitation, and delusion are undesirable psychological signs of serious intoxication that can be treated with supportive treatment.

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