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Global Health Impact of Major Classes of "Designer Drugs": Structural, Pharmacological and Toxicological Overview

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Abstract

Different botanical derived or synthetic addictive substances have been "misused" and/or "abused" for centuries around the world. To overcome the abuse by these substances, strict legal laws were constituted globally. However, novel and drugs with chemical structures similar to illegal psychoactive drugs substances (with a slight structural change) were manufactured in undercover laboratories to have the same or augmented psychostimulatory effects. Currently, the major classes of designer drugs are piperazines, cathinones, synthetic cannabinoids, synthetic opioids, tryptamines, and phenethylamines.

These classes of designer drugs have shown to elicit significant psychostimulatory effect by a different mechanism of action. They have shown to affect various monoaminergic neurotransmission and induce severe toxic effect, which if not treated properly, can be detrimental leading to death. In this book chapter, we have explained the chemical structural aspects of various designer drugs, their mechanism of action, side-effect and possible therapeutic interventions.

Keywords: Designer drugs; Piperazines; Cathinones; Synthetic cannabinoids; Synthetic opioids; Tryptamines; Phenethylamines

Introduction

History and current scenario of drugs of abuse

Drug addiction rates and deaths resulting from drug abuse has become a huge problem worldwide. In the United States, which is one of the largest countries in terms of percentage mortality rate due to substances of abuse, 1 of every 20 deaths connects to addiction [1,2]. Despondently this addiction epidemic is also found Europe, Asia, Australia and Africa. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) discovers a new legal high drugs-numbers of novel drugs have raisin from 14 in 2005 to 300 in 2014 [3-5]. Historically, designer drugs or Novel psychoactive substances began to be used in the late 1960s as substitutes for banned control substances. Designer drugs are substances manufactured with a slight change in chemical structures that similar to illegal psychoactive drugs, for the purpose of marketing and avoid interdiction from authorities. Interestingly, designer drugs were synthesized by pharmaceutical companies with the ultimate goal of therapeutic interventions for various central nervous system and peripheral disorders, but abuse liability proved as the collateral. Therefore, the United

State authorities in 1970 founded the Controlled Substances Act, which is a legal system to identify and organize abuse substances, depending on the medical value, abuse possibility, and physiological physical effects. The Controlled Substances Analogue Enforcement defined the designer drugs as "a substance other than a controlled substance that has a chemical structure substantially similar to that of a controlled substance in schedule I or II or that was specifically designed to produce an effect substantially similar to that of a controlled substance in schedule I or II." The Controlled Substances Act divide the Substances

of Abuse into 5 classes, in 1 to 5 scales, where Class-I is having a great risk of abuse, and 5 is having the minimal risk of abuse. First termed designer drugs were in 1988 on a compound called "China White" which is a synthetic opioid [6]. In the recent times, trading and embracing of these drugs have increased because of the Internet (the main marketer of such drugs of various kinds). Designer drugs industry depends on two main sources; plant, where the raw materials are taken and then hidden laboratories that synthesize the final product [7]. The final product is often marketed as unfit for human consumption, also attempting to cheat for distribution purpose as scientific laboratory materials or plant supplements [4]. Addictive drugs are known to humans since the mid-19th century, where humans began to extract morphine from opium. Then at the beginning of 1900, heroin was produced and this was followed by cocaine. Development in the pharmaceutical field led to heightened and intensified production of more potent and intoxicating drugs.

These new designer drugs have substantial psychological properties which cause significant abuse potential. With growing addiction problem, countries have developed severe legislations that limit the abuse of drugs [8].

Conversely, the emergence of new legislation motivates clandestine laboratories to synthesize new and novel kinds of drug analogues called designer drugs. The industry of designer drugs often develops in countries that contain manpower with various skills which range from experienced chemists to cheap labor, and this yields to low overall production cost. For example, simple online search on designer drugs leads to the learning method of synthesis and use [4,9]. Most of the current designer drugs products are synthesized in China, Mexico, and southeast Asian countries. The main source of designer drug business is the internet, followed by nightclubs and head shops which act as potential distributors. Distributors of these designer drugs intentionally add signs showing invalid for human consumption or fraud expression on packages that deliver to users Phrases like legal high, or legal drugs used to deceive consumers consequently making series complications among societies [10].

The affordable price of the designer drugs ranges between 6 to 12 pounds for each pack and each collection has 1 to 6 tablets. Estimated profits are extremely lucrative, as one kilogram of the material cost thousands of dollars as profit returns to distribute up to $20 million [11,12]. In 2010 a study done by [13], illustrated the ease and simplicity of purchasing 26 brands of synthetic drugs from the popular website in the UK. Thus, the Internet makes the abuse for these designer drugs to become readily accessible to the public. There are insufficient databases or scientific literature on the pharmacology and toxicity profile of designer drugs. Additionally, healthcare professionals face huge difficulties to distinguish between many kinds of designer drugs. Most of these compounds cannot be readily detected by immunoassays, urine screens, but are detected by gas chromatography and mass spectrometry [14-16]. Hence, in this chapter, we have elucidated the pharmacological effects, toxicity profile and appropriate therapy for various designer drugs.

Designer drugs

Novel psychoactive substances are classified into two categories; based on the mental impact (stimulants, or hallucinogens) and based on their chemical structures [5]. The most common chemical structure for designer drugs are Phenethylamines, Piperazines, Tryptamines, Synthetic cannabinoids, Synthetic cathinones and Synthetic opioids (Figure 1). Statistics indicate that numbers of new psychoactive substances in continuous raise since 2009. Percentage of newly discovered substances between 2009-2012 are as follow 23% for Phenethylamines and Synthetic cannabinoids, 18% Synthetic cathinones, 10% Tryptamines, and 5% piperazines. This study also concluded that the most founded substance belongs to piperazines and cathinone compounds.

Piperazines designer drugs

At the beginning of the Millennium, Piperazines derivatives were known as a new drug of abuse since 3,4-methylenedioxymethamphetamine (MDMA) was banned by the authorities. Piperazines compounds do not exist naturally, but it is completely synthesizing in the chemical laboratories. Many industrial processes involve piperazines compounds such as insecticides, in hardener of epoxy resins, accelerators for rubber. In the medical field, piperazines were used as raw material to synthesize fluoroquinolone drugs [17,18]. Piperazines have similar stimulant effects comparable to amphetamine with additional euphoric effect. Consequently, this gained the widespread popularity of piperazines around the world [19,20]. Internet is the main source of distribution for piperazines compounds under different names like; "party pills" or "legal Ecstasy", "Head Rush", "XXX"," Strong as Hell"," Herbal ecstasy"," "A2", and "Legal E." [4,20]. Piperazines products are considered from the top-selling psychological drugs through the internet, especially in New Zealand,

Europe, and North America. As a result, there is huge profit comes as a result of that wide distribution, in New Zealand, the annual financial revenue of the BZP sale is estimated at NZ$50 million [21].

The most well-known drugs of abuse belong to this group are benzylpiperazines BZP, 1-(3-trifluoromethylphenyl) piperazine TFMPP, 1-(3,4-methylenedioxyphenyl) piperazine (MDBP), and 1-(3-chlorophenyl) piperazines (mCPP) [22,23]. Piperazines was abused to increase alertness, reinforce mental and physical ability [24-27]. The common routes of administration for piperazines derivatives are oral as tablets, capsules, also as a powder or liquid form [28]. Although the United States authorities placed

BZP under Schedule I controlled substance in 2004, a number of seized BZP samples continued to rise [20]. Most of the reserved samples contain a mix of piperazines compounds, BZP with TFMPP, or with other psychoactive like amphetamine or cocaine [29].

Chemical structures and pharmacology of piperazines

Piperazine is a cyclic organic compound with two opposing nitrogen atoms within a six-membered ring. Chemical structures of piperazines are not related to other psychoactive substances [30]. There are two classes for piperazines derivatives; benzylpiperazines. The benzylpiperazines include N-benzylpiperazine (BZP) and 1-(3,4-methylenedioxybenzyl)-piperazine (MDBP), the methylenedioxy analogue. And phenylpiperazines such as 1-(3-chlorophenyl) piperazine (mCPP), 1-(3-trifluoromethylphenyl) piperazines (TFMPP), and 1-(4methoxyphenyl) piperazine (MeOPP) [19,30] (Figure 2). At first, piperazines were designed to cure intestinal roundworm and tapeworm, as anthelminthic by researchers from Burroughs Wellcome & Co. Between the 1970s and 1980s, there were few drug trials to validate the antidepressant effects following the results of addiction [4,31,32]. Piperazines have interaction with sero-

tonin receptors leading to psychoactive properties. It also has stimulant and hallucinogenic effects due to increase the levels of the monoamines (dopamine and serotonin) in CNS. BZP is a sympathomimetic stimulant (amphetamine-like effect), release dopamine, serotonin, and adrenaline in CNS, and inhibit the reuptake of dopamine. It is found as dihydrochloride salt, white powder, or as a free base with pale yellow color.

Dosage of abuse ranges from 50 to 250mg, with the onset of duration last for 6-8 hrs. BZP can cross the blood-brain barrier and the onset of action for BZP takes 2 hours to start and has the stimulatory action for 4-8 hours the influence and this result in multiple doses by users. Elimination half-life is 5.5 hrs with 30 hrs possibility to detect in plasma. The liver is considered the main site of metabolism by hydroxylation and N-dealkylation catalyzed by cytochrome P450 [3,30,31,33]. Drug interaction could happen with other drugs due to inhibiting cytochrome oxidase isoenzymes [34].

Trifluoromethylphenylpiperazine (TFMPP) is phenylpiperazines which act as non-selective serotine receptors agonist and also elevate release of serotonin by blocking the reuptake. TFMPP has a minimal effect on dopamine and noradrenaline release [35,36]. TFMPP derivative (5-100mg) is found as powder, tablet, or capsule and usually in combination with other psychostimulants [37,38]. Initial metabolism of TFMPP occurs by hydroxylation with CYP2D6 and phase 2 metabolism by glucuronidation, sulfation andAcetylation [39]. As an alternative for MDMA, BZP and TFMPP combined products (2:1) are available. In these combined products, BZP promotes the stimulant influence, while the TFMPP provide the hallucination effect [38,40,41].

Toxicity and treatment of piperazines

Usually with minimal dosage piperazines lead to stimulant influence, while with high dose exhibit hallucination and sympathomimetic toxidrome [37,42,43]. Piperazines compounds exhibit amphetamine-like stimulant effect and with the same abuse possibility. Combination of BZP with TFMPP result in MDMA like sympathomimetic action and this can lead to life-threatening serotonin syndrome. Due to the easy permeability through the blood-brain brier, the clinical manifestations of the CNS intoxications include anxiety, headache, paranoia, tremors, and insomnia. Piperazines synthetic drugs also affect the peripheral nervous system include vomiting, palpitations diaphoresis, sinus tachycardia, metabolic acidosis, hyperthermia, auditory and visual hallucinations, vasoconstriction, ischemia, tachycardia and arrhythmia of cardiovascular. Upon consumption of high doses of piperazine, the severe toxic effects include; multi-organ failure, seizure psychosis, renal toxicity, respiratory acidosis, hyponatremia [17,44,45]. Normal detection methods such as urine immunoassay usually give a negative result. However, gas chromatography and mass spectrometry are the most useful technology to identified piperazines compounds [46,47]. Currently, there is no special antidote for the piperazines toxicity. Nevertheless, the current approaches are to provide supportive care and monitoring the vital sign is the first step of patient care. Benzodiazepines are the first line of therapy to treat seizure and agitation associated with piperazine toxicity. Charcoal for oral ingestion toxicity, IV fluids, and rapid cooling strategies are the other pharmacological and non-pharmacological approaches to reduce the piperazine-induced toxicity [4,37,48,49]. Furthermore, as a safety precaution, patients should receive electrocardiogram test.

Cathinones designer drugs

For centuries, people in Arabic peninsula and East Africa have used a green plant called as “Khat”. Khat has been found in medicinal and botanical literature since the eleventh century. Remarkably, people in Yemen and Somalia are still consuming (chew the leaves) Khat for its amphetamine-like influence [20,50]. Cathinone is the main molecule in Khat and the first synthesized compound related to cathinone was methcathinone in 1928. Synthetic cathinone (Bath Salt) and tits structurally related group of drugs gained fame in the early 1990s as drugs of abuse [20,51]. In 2014, around numerous patients were hospitalized in the United States related and relatively substantial number (52%) of cases were linked to cathinone [52]. The most recognized products of the Cathinone derivatives are (Figure 3);

- 4-methyl-N-methylcathinone (mephedrone),
- 3,4-methylenedioxy-N-methylcathinone (methylone),
- 3,4-methylenedioxypyrovalerone (MDPV)

Trade names for cathinones Meow Meow, MCAT, ‘Ivory Wave’, ‘White Lightning’ and ‘Vanilla Sky’ [53]. The distribution process usually come in form of capsule, pills, or powder which is the most common form, with different rout of administrations [54].

Chemical structure and pharmacology of cathinones

Cathinone derivatives belong to phenylalkylamine and naturally appears as alkaloid beta ketoamphetamine, analogue to MDMA and methamphetamine, [51,55]. Synthetic cathenones compounds are hydrophilic due to the presence a ketone group on beta-carbon. This chemical structures makes cathinones less permeable to CNS, as result, abusers attend to raise the dose of cathinones drugs [56]. The potential mechanisms of action of cathinone derivatives are similar to amphetamine because of the similarity between structures. Cathinone compounds exhibit sympathomimetic action and also cause reuptake inhibition of dopamine, serotonin, and norepinephrine within the central nervous system. In addition, cathinones lead to elevated monoamines release from the presynaptic neurons [57,58]. Orally dose of mephedrone range from 100-200mg, with the onset of effect between 30-45 minutes and extend the duration of action for 2-5hrs. MPDV has shown to exhibit more strength and extent of abusive action [59].

Toxicity and treatment of cathinones

Clinical features of bath salt toxicity are usually connected to sympathomimetic symptoms (cardiovascular and neurological). Neurological adverse effects include agitation, anorexia, insomnia, paranoia, psychosis. In addition, the patients also experience a headache, palpitation and chest pain [60,20]. The cardiovascular toxicity includes hypertension, tachycardia, hyperthermia, cardiovascular collapse and myocardial infarction [61].

Cathinone compounds cannot be detected by immunoassay urine screens but identified and detected using gas chromatography and mass spectrometry [62,63]. Considering that cathinones are analog to methamphetamine, abusers after stop using cathinone compounds may have a risk of Parkinson disease as a cause of decline in the activity of dopamine in the basial ganglia [64]. Management of cathinones toxicity is limited and there are limited literatures currently. At this time, supportive therapy

mainly provides to patients with some medications such as IV fluid, benzodiazepine (to cure hyperthermia, agitation, and seizure) to overcome problems [4,61,65].

Synthetic cannabinoids designer drugs

During the era of the 1960s, a group of researcher's accidentally invented the synthetic cannabinoids [66]. The scientists were trying to improve the therapeutic features of the natural cannabinoids D9-tetrahydrocannabinol (D9-THC) and that yielded synthetic Cannabinoids [4]. Since the early 2000s, there are hundreds of new Synthetic Cannabinoids available on the internet and like other designer drugs; most of the synthetic cannabinoids are manufactured in China. Synthetic Drug Abuse Prevention enacted in 2012 and listed 15 of the synthetic cannabinoids as Schedule-1, and four years later the department added 47 new compounds [67]. Manufacturing of synthetic cannabinoids are mostly combined with natural herbs (marijuana) to delude and the abusers smoke it [61]. Synthetic cannabinoids are referred as Fake marijuana, spice, K2, [67].

Chemical structures and pharmacology of synthetic cannabinoids

Structurally cannabinoids are classified as seven classes; classical cannabinoids (HU-210), naphthoylindoles (JWH-018 and JWH-073), naphthylmethylindoles, napththoylpyrroles, phenylacetylindoles (JWH-250), cyclohexylphenols (CP 47-497), and naphthylmethylindenes [4,66,68,69] (Figure 4). The synthetic cannabinoid has a stronger effect up to 800 times by comparing to natural cannabinoids. The naturally occurring D9-THC acts as partial agonist on Cannbinoid-1 receptor (CB1), while the synthetic cannabinoids act as a full agonist on the CB1 receptor [67,70]. CB1 and CB2 receptors are G protein receptors the main component of endocannabinoid system inside the brain [71]. CB1 located in the central nervous system modulates GABA and glutamate neurotransmission and is responsible for the psychoactivity of cannabinoids. CB2 receptors are in the peripheral nervous system and are responsible for the immunomodulatory effect of cannabinoids [72,73]. Since the synthetic cannabinoids are full agonist on CB1 receptor, the onset of duration will prolong the risk of adverse effects [74,75].

Toxicity and treatment of synthetic cannabinoids

Symptoms of synthetic cannabinoids toxicity include anxiety, agitation, paranoia, delusions, aggression, paranoid thinking and anxiety. In addition, the patient usually has feelings of energy, euphoria, mild sedation, nausea, vomiting, hyperemesis, and abdominal pain [4,67,76,77]. Cannabinoids compounds cannot be detected by immunoassay in urine screens, but by using gas chromatography and mass spectrometry it can be identified [78]. Treatment for synthetic cannabinoid toxicity depends on monitoring of vital signs and providing supportive care to patients with intoxication. The drug of choice for both adverse side effects and seizures are benzodiazepines [5,79].

Synthetic opioids designer drugs

In the United States, there are approximately 12.5 million people who use pain medication incorrectly by a national survey conducted in 2015. Great demand and huge percentage of profit, 1kg of fentanyl can make 20 $million) [80]. In 2014, around 29, 000 victims have been died due to this problem [81]. Sadly, opiates are responsible for 60% of overdose deaths [61,82]. Similar to the other designer / abusive drugs, clandestine laboratories mainly in China manufacture the synthetic opioids The most known synthetic opioids are fentanyl, fentanyl analog, and novel synthetic opioids like U-47700, which recently introduced to schedule 1 by DEA 2016 [83]. Currently, the world's focus is related to the opioid epidemic problem.

Chemical structures and pharmacology of synthetic opioids

Paul Janssen discovered fentanyl compound in 1960, primarily to treat patients with pain. "China white" or synthetic heroin (alpha-methylfentanyl (AMF) was the first analogue that was synthesized in California 1979. Fentanyl and its analogs have a different chemical structure as compared to opiates, but exhibit similar pharmacological action as of opiates. After FDA approval in 1972, Fentanyl was used in the United States as anesthetics. The potency of fentanyl is around 100 times more than morphine and it has 40 minutes duration of action [7,84]. Fentanyl can couple with G-protein receptors and act as a full agonist of μ-opioid receptors. It inhibits ascending pathway of pain and raise the pain threshold (Figure 5).

Toxicity and treatment of Synthetic opioids: Synthetic opioids can be administered by various routes, inhalation, the powder, oral, nasal insufflation, rectal, and IV injection [85,86]. The most serious toxic effects of fentanyl are respiratory depression as other opiates. In addition, fentanyl abuse leads to opioid toxidrome-bradycardia, loss of consciousness, cyanosis, and miosis [87]. Additional clinical features include hypotension, pulmonary edema, ileus, nausea, pruritus, cough suppression, orthostatic hypotension, urinary urgency or retention, and chest wall rigidity, particularly with IV usage [82]. Opioids cannot be detected by immunoassay in urine screens, but by using gas chromatography and mass spectrometry can be identified [88]. With regard to opioid abuse, the patients are monitored for breathing (maintain proper airway). The airway maintenance is considered as the first step in providing care to patients. After the proper maintenance of airway, naloxone (opioids antagonist) is administered to reverse the opioid-induced toxicity [80,89].

Tryptamines designer drugs

Serotonin is one of the most important transmitters involved in controlling many significant processes like sleep, memory, behavior, and temperature regulation. In fact, serotonin is a tryptamine derivative which is found inside the human brain with a limited amount and is significantly higher in the periphery. In 1958, scientists discovered natural sources of tryptamines compounds and this was found in fungi (*Psilocybe cubensis*) and botanicals [90]. The psychoactive influence of tryptamines has been known since the ancient times through the magic mushrooms [56]. The synthetic tryptamines have been traced to the 1960s (alfa-Methyltryptamine-AMT) where it was used as an antidepressant by Soviets [91]. In recent times, in the United Kingdom, numerous cases of hallucination has been associated with the abuse of tryptamines. The most known drugs of abuse belonging to tryptamines are the alpha-methyltryptamine (AMT), 4-hydroxy-N-methyl-N-ethyltryptamine (4-HO-MET) and Dimethyl-tryptamine (DMT). Tryptamines products are usually distributed in the form of powder or tablets. There are many different ways of tryptamines consumption like smoking, insufflation, IV or IM injection [56,92]. Accessible methods of synthesis from internet make tryptamines a very popular designer drug, especially among young adults [90,93,94].

Chemical structures and pharmacology of tryptamines

Tryptamines are monoamine alkaloids derived from the ami-

no acid tryptophan [93,95]. Indole structure is the backbone of tryptamines compounds and this is the site at which the synthetic modifications occur for the scheming various designer drugs [95,96]. Hallucination is considered as the key effect of tryptamines abuse comparatively to stimulant actions. Tryptamines are serotonin 2A receptor agonist. Often the onset of duration for tryptamines is low, that forces the abuser to elevate the dose resulting in adverse effects [97-99] (Figure 6).

Toxicity and treatment of tryptamines

Clinical features of tryptamines misuse/ overdose include tachycardia, tachypnea, hypertension, trismus (lock jaw), anxiety, euphoria, sweating, diarrhea, nausea, vomiting, abdominal pain, sialorrhea, diaphoresis, palpitations, drowsiness, dysphoria, serotonin syndrome and hyperthermia [91,100-103]. Similar to the designer drugs, there is no precise antidote to cure tryptamines intoxication. Supportive care and vital signs monitoring are the first line therapy provide to patients [90-104].

Phenethylamines (2Cs) designer drugs

Phenethylamines are a large group of drugs that contain different kinds of synthetic compounds. Designer drugs that belong to this group structurally have two carbon atoms located between the benzene ring and an amino group.

In the late 1850s, old synthetic phenethylamines were synthesized and this included Amphetamine (α-methylphenethylamine; α-methylbenzeneethanamine), methamphetamine (α, N-dimethylphenethylamine). Many years later (in 1912), 3,4-methylenedioxymethamphetamine (MDMA) was synthesized to help people to decrease their appetite [105]. These drugs are considered as old fashion phenethylamines. The new synthetic 2Cs was introduced after Alexander Shulgin released a book which started a sparkle phenomenon in designer drugs world. PIHKAL is an acronym representing "Phenethylamines I Have Known and Loved". This book explained in detail the synthesis of over 200 phenthylamine compounds. Drugs like 2,5-dimethoxy-4-ethylphenethylamine (2C-E, Europa), 2,5-dimethoxy-4-ethylthiophenethylamine (2C-T-2), 2,5-dimethoxy-4-(n)-propylthiophenethylamine , Blue Mystic, T7, Beautiful, Tripstay, Tweety-Bird Mescaline), 4-iodo-2,5-dimethoxyphenethylamine (2C-I, i), and 4-iodo-2,5dimethoxy- N-(2-methoxybenzyl) phenethylamine (25I-NBOMe) were mentioned in this book. Since 2011, 2C-I-NBOMe had spread around the world and has different streets name like Smiles, N-Bomb, Pandora and Dime. This designer drug can be found online, head shops and even gas stations [4,106].

Chemical structures and pharmacology phenethylamines (2Cs)

The 2Cs designer drugs show high affinity to serotonin, alpha-adrenergic and dopamine receptors with different agonist and antagonist activities. MDMA is acting by elevating the release of monoamines (serotonin, adrenaline, and dopamine) from their terminal synapse, while appose their reuptake [107,108]. Phenethylamines come as a powder, capsules, tablets, or in liquid form. Routes of administration are oral, inhalation, nasal insufflation, or intravenous injection. The oral route of phenethylamines is considered slower in effect than the insufflation route. The onset of action of oral phenethylamines ranges from 1 to 2.5 hours and duration of action 5-7 hours, while the insufflation takes 10-15 minutes and has a duration of action 2-4 hours [109]. Phenethylamines produce stimulant effects at low doses lead to raise the activity and elevate the alertness of various (increased arousal and alertness). However, the undesirable effect of hallucination and sympathomimetic related adverse effects become after a high dose of 2Cs [110,106) (Figure 7).

Toxicity and treatment of phenethylamines

Symptoms of phenethylamines toxicity include tachycardia, hyperthermia, hypertension, euphoria, empathy, nausea, vomiting, agitation, delirium, respiratory depression, mydriasis, paranoia, dysphoria, severe confusion, and seizures [111]. Other adverse effects of phenethylamines include jaw clenching, muscular tension, tooth grinding and constant restless movement of the legs and increased muscle activity [112-115]. Phenethylamines long-term side effects also include memory deterioration, impaired mental skills, frequent paranoia and severe depression [116-118]. Treatment depends on monitoring vital signs; provide supportive care to a patient with intoxication. Drug of choice for both adverse side effects and seizures are benzodiazepines also can be used to treat agitation, hypertension, tachycardia, and hyperthermia [119-120].

Conclusion

Designer drugs are abused in order to experience psychostimulant effects similar the legally banned substances of abuse (heroin or cocaine). Numerous people around the world are currently abusing the designer drugs. Substantial health impairments have been observed globally due to the abuse of designer drugs. These products are presently produced by clandestine labs in the U.S and other countries around the world. Designer drugs are currently sold by independent dealers in different formulations (powdered form, in single-component tablets, capsules, or in combination combined with MDMA or other illicit controlled substances through the internet and retail stores. The most common route of administration by the abusers are an oral route (ingest), inhale, inject, smoke, or snort. Due to the structural and chemical characteristic features (lipophilicity), these designer drugs readily cross the blood-brain barrier and also be readily distributed throughout the body.

Hence, it exerts an effect throughout the body on different organ systems. The biogenic monoaminergic neuronal tract and peripheral sympathetic nervous system are extensively affected by the designer drugs abuse which can lead to behavioral changes (memory deficit, mental disorders and movement impairment) and further increase the risk for neurological disorders such as Parkinson's disease (movement disorder), dementia (memory disorder) and various other mental disorders (psychosis, ADD and depression). Hence, if this epidemic is not controlled appropriately, it can cause a huge economic impact and decline in the health of the current and future generation

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Figures

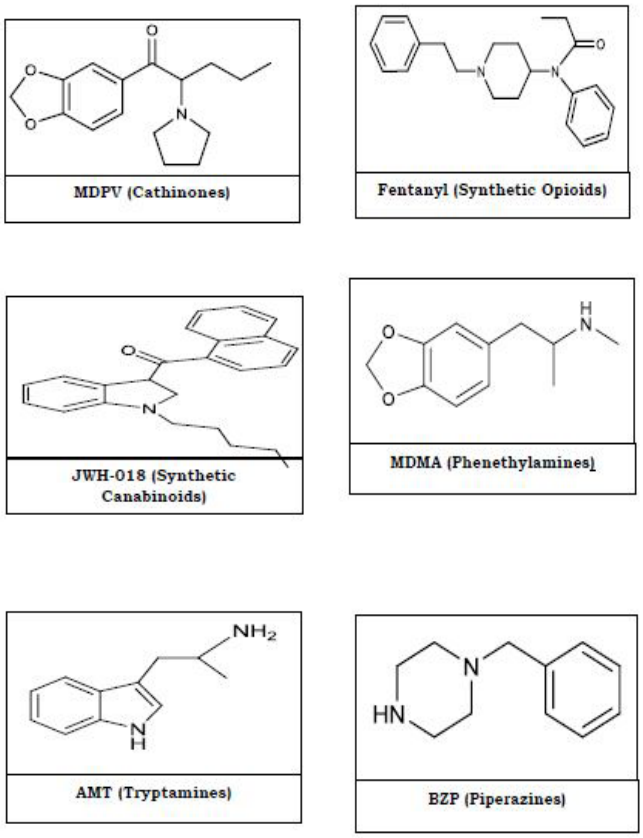
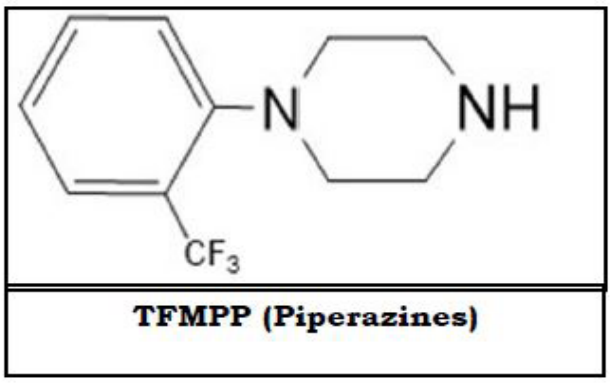


Figure 1: List of Various Designer Drugs



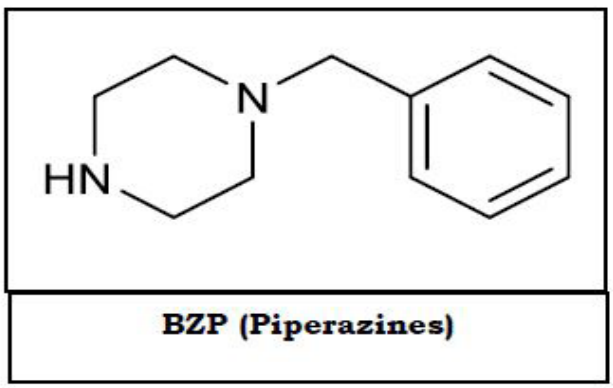


Figure 2: Designer drugs: Piperazine derivatives

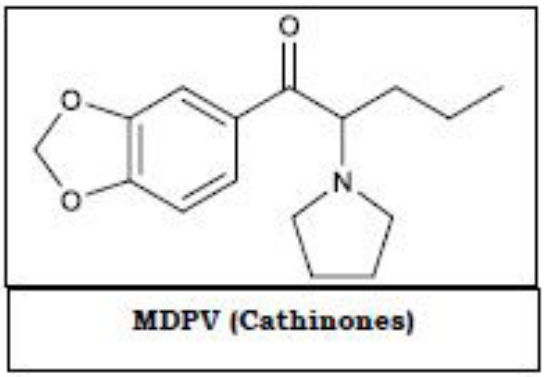


Figure 3: Cathinone Designer drug

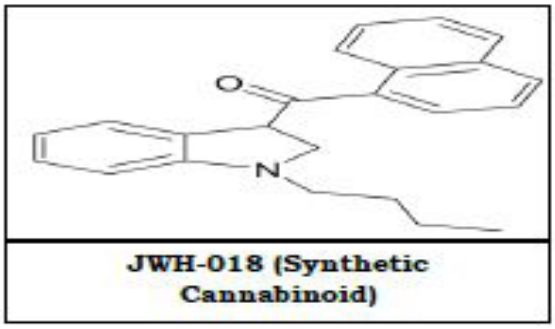


Figure 4: Synthetic Cannabinoid Designer Drug

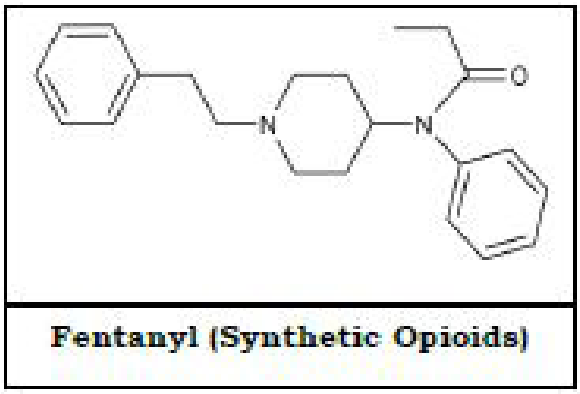


Figure 5: Synthetic Opioid Designer drug

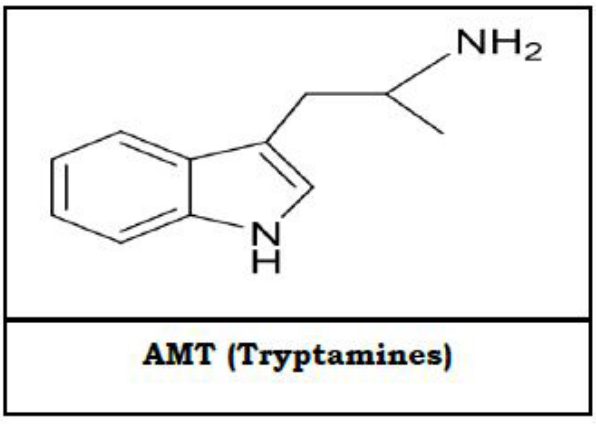


Figure 6: Tryptamine Designer drug

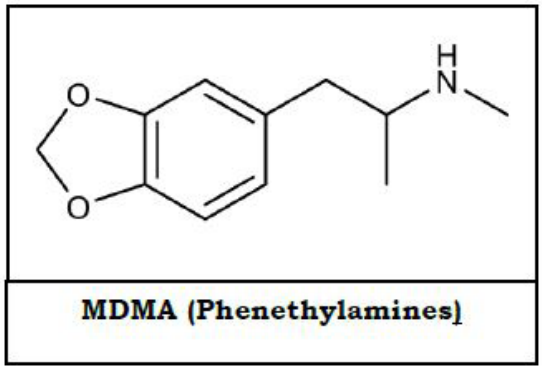


Figure 7: Phenethylamine Designer drug

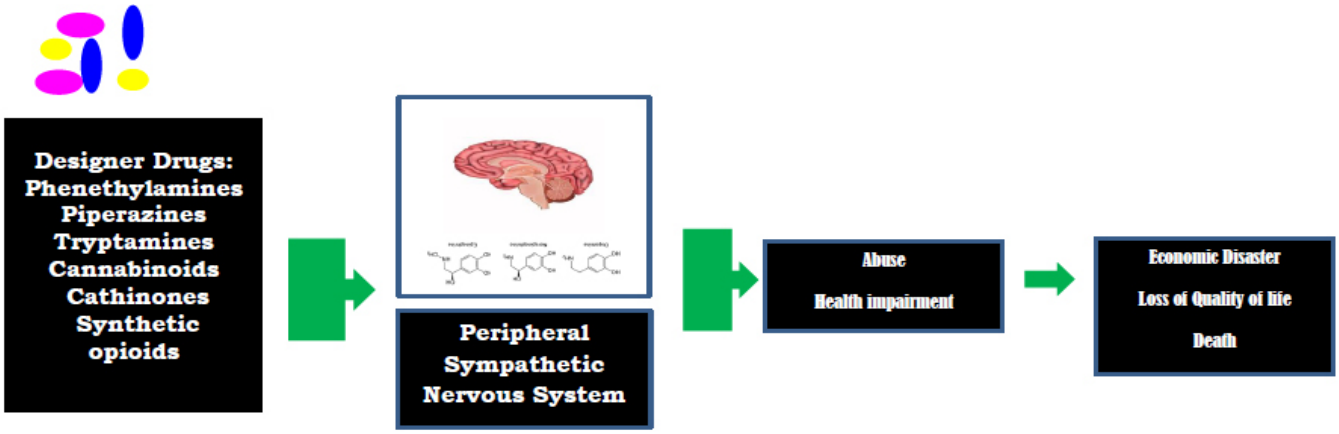


Figure 8: Designer Drugs mediated health impairment

References

1. World Health Organization. WHO expert committee on drug dependence. World Health Organ Tech Rep Ser. 2012; 973: 1-26.
2. Report D. World drug report. Trends in Organized Crime. 1997; 3: 11-14.
3. Hill SL, Thomas SHL. Clinical toxicology of newer recreational drugs. Clin Toxicol (Phila). 2011; 49: 705-719.
4. Musselman ME, Hampton JP. "not for human consumption": A review of emerging designer drugs. Pharmacotherapy. 2014; 34: 745-757.
5. Liechti ME. Novel psychoactive substances (designer drugs): Overview and pharmacology of modulators of monoamine signalling. Swiss Med Wkly. 2015; 145: 1-12.
6. Kram TC, Cooper DA, Allen AC. Behind the identification of China White. Anal Chem. 1981; 53: 1379A–1386A.
7. Henderson G. Designer Drugs: Past History and Future Prospects. J Forensic Sci. 1998; 33: 569-575.
8. Chavan S, Roy V. Designer Drugs: a Review. World J Pharm Pharm Sci. 2015; 4: 297-336.
9. Madras B. Designer Drugs: An Escalating Public Health Challenge. GlobaldrugpolicyInfo. 2012; 1-57.
10. Corazza O, Simonato P, Corkery J, Trincas G, Schifano F. "Legal highs": safe and legal "heavens"? A study on the diffusion, knowledge and risk awareness of novel psychoactive drugs among students in the UK. Riv Psichiatr . 2014; 49: 89-94.
11. Sellers EM. Deconstructing Designer Drugs. Clin Pharmacol Ther. 2017; 101: 167-169.
12. Huestis MA, Tyndale RF. Designer Drugs 2.0. Clin Pharmacol Ther. 2017; 101: 152-157.
13. Davies S, Wood DM, Smith G, Button J, Ramsey J, Archer R, et al. Purchasing "legal highs" on the Internet--is there consistency in what you get? QJM . 2010; 103: 489-493.
14. Weaver MF, Hopper JA, Gunderson EW. Designer drugs 2015: assessment and management. Addict Sci Clin Pract. 2015; 10: 8.
15. Assi S, Gulyamova N, Ibrahim K, Kneller P, Osselton D. Profile, effects, and toxicity of novel psychoactive substances: A systematic review of quantitative studies. Hum Psychopharmacol. 2017; 32: 1–7.
16. Zamengo L, Frison G, Gregio M, Orrù G, Sciarrone R. Determination of illicit drugs in seized materials: Role of sampling and analysis in estimation of measurement uncertainty. Forensic Sci Int . 2011; 208: 108-123.
17. Nikolova I, Danchev N. Piperazine Based Substances of Abuse: A new Party Pills on Bulgarian Drug Market. Biotechnol {&} Biotechnol Equip. 2008; 22: 652-655.
18. Dessouky YM, Ismaiel SA. Colorimetric determination of piperazine in pharmaceutical formulations. Analyst. 1974; 99: 482–486.
19. Arbo MD, Bastos ML, Carmo HF. Piperazine compounds

as drugs of abuse. Drug Alcohol Depend. 2012; 122: 174-185.

20. Rosenbaum CD, Carreiro SP, Babu KM. Here Today, Gone Tomorrow. and Back Again? A Review of Herbal Marijuana Alternatives (K2, Spice), Synthetic Cathinones (Bath Salts), Kratom, Salvia divinorum, Methoxetamine, and Piperazines. J Med Toxicol. 2012; 8: 15-32.

22. Wilkins C, Girling M, Sweetsur P, Huckle T, Huakau J. Legal party pill use in New Zealand. Cent Soc Heal Outcomes Res Eval. 2006; 1-62.

23. Yeap CW, Bian CK, Fahmi A, Abdullah L. A Review on Benzylpiperazine and Trifluoromethylphenypiperazine: Origins, Effects, Prevalence and Legal Status. Heal Environ J. 2010; 1: 38-50.

24. Drug Enforcement Administration (DEA), Department of Justice. Schedules of controlled substances; placement of 2,5-dimethoxy-4-(n)-propylthiophenethylamine and N-benzylpiperazine into Schedule I of the Controlled Substances Act. Final rule. Fed Regist. 2004; 69: 12794-12797.

25. Cohen BMZ, Butler R. BZP-party pills: a review of research on benzylpiperazine as a recreational drug. Int J Drug Policy. 2011; 22: 95-101.

25. Gaia Vince. Mind-altering drugs: does legal mean safe? New Scientist. 2006.

26. Davies S, Wood DM, Smith G, Button J, Ramsey J, Archer R, et al. Purchasing "legal highs" on the Internet-is there consistency in what you get? Qjm. 2010; 103: 489-493.

27. Austin H, Monasterio E. Acute Psychosis Following Ingestion of "Rapture." Australas Psychiatry. 2004; 12: 406-408.

28. Gee P, Richardson S, Woltersdorf W, Moore G. Toxic effects of BZP-based herbal party pills in humans: A prospective study in Christchurch, New Zealand. N Z Med J. 2005; 118: 8716.

29. Kenyon S, Button J, Ramsey J, Holt, David W (Analytical Unit, St Georges, University of London U. Poster: "Legal highs" - Analysis of tablets and capsules containing piperazines. Anal Unit, St Georg Univ London. 2006; 118: 2006.

30. Katz DP, Deruiter J, Bhattacharya D, Ahuja M, Bhattacharya S, Clark CR, et al. Benzylpiperazine: "A messy drug". Drug Alcohol Depend. 2016.

31. Bye C, Munro-Faure AD, Peck AW, Young PA. A comparison of the effects of 1-benzylpiperazine and dexamphetamine on human performance tests. Eur J Clin Pharmacol. 1973; 6: 163-169.

32. Campbell H, Cline W, Evans M, Lloyd J, Peck AW. Comparison of the effects of dexamphetamine and 1-benzylpiperazine in former addicts. Eur J Clin Pharmacol. 1973; 6: 170-176.

33. Antia U, Lee HS, Kydd RR, Tingle MD, Russell BR. Pharmacokinetics of "party pill" drug N-benzylpiperazine (BZP) in healthy human participants. Forensic Sci Int. 2009; 186: 63-67.

34. Antia U, Tingle MD, Russell BR. Metabolic interactions with piperazine-based "party pill" drugs. J Pharm Pharmacol. 2009; 61: 877-882.

35. Zuardi AW. 5-HT-related drugs and human experimental anxiety. Neurosci Biobehav Rev. 1990; 14: 507-510.

36. Kennett GA, Whitton P, Shah K, Curzon G. Anxiogenic-like effects of {{}mCPP{}} and {{}TFMPP{}} in animal models are opposed by 5-{{}HT{}}1C receptor antagonists. Eur J Pharmacol. 1989; 164: 445-454.

37. Schep LJ, Slaughter RJ, Vale JA, Beasley DMG, Gee P. The clinical toxicology of the designer "party pills" benzylpiperazine and trifluoromethylphenylpiperazine. Clin Toxicol. 2011; 49: 131-141.

38. Curley LE, Kydd RR, Robertson MC, Pillai A, McNair N, Lee H, et al. Acute effects of the designer drugs benzylpiperazine (BZP) and trifluoromethylphenylpiperazine (TFMPP) using functional magnetic resonance imaging (fMRI) and the Stroop task--a pilot study. Psychopharmacology (Berl). 2015; 232: 2969-2980.

39. Staack RF. Piperazine designer drugs of abuse. Lancet. 2007; 369: 1411-1413.

40. Herndon JL, Pierson ME, Glennon RA. Mechanistic investigation of the stimulus properties of 1-(3-trifluoromethylphenyl) piperazine. Pharmacol Biochem Behav. 1992; 43: 739-748.

41. Lin JC, Jan RK, Kydd RR, Russell BR. Subjective effects in humans following administration of party pill drugs BZP and TFMPP alone and in combination. Drug Test Anal. 2011; 3: 582-585.

42. Staack RF, Maurer HH. Metabolism of designer drugs of abuse. Curr Drug Metab. 2005; 6: 259-274.

43. Antia U, Tingle MD, Russell BR. Metabolic interactions with piperazine-based "party pill" drugs. J Pharm Pharmacol. 2009; 61: 877-882.

44. Gee P, Jerram T, Bowie D. Multiorgan failure from 1-benzylpiperazine ingestion legal high or lethal high. Clin Toxicol. 2010; 48: 230-233.

45. Gee P, Richardson S, Woltersdorf W, Moore G. Toxic effects of BZP-based herbal party pills in humans: A prospective study in Christchurch, New Zealand. N Z Med J. 2005; 118.

46. McNamara S. 1-benzylpiperazine (BZP) abuse amongst attendees of the Drug Treatment Centre Board. Ir Med J. 2009; 102: 191.

47. Dickson AJ, Vorce SP, Holler JM, Lyons TP. Detection of 1-benzylpiperazine, 1-(3-trifluoromethylphenyl)-piperazine, and 1-(3-chlorophenyl)-piperazine in 3,4-methylenedioxymethamphetamine-positive urine samples. J Anal Toxicol. 2010; 34: 464-469.

48. Balmelli C, Kupferschmidt H, Rentsch K, Schneemann M. [Fatal brain edema after ingestion of ecstasy and benzylpiperazine]. Dtsch Med Wochenschr. 2001; 126: 809-811.

49. Wood DM, Dargan PI, Button J, Holt DW, Ovaska H, Ramsey J, et al. Collapse, reported seizure—and an unexpect-

ed pill. Lancet. 2007; 369: 1490.

50. Brenneisen R, Fisch H, Koelbing U, Geisshusler S, Kalix P. Amphetamine- like effects in humans of the khat alkaloid cathinone. Br J Clin Pharmacol. 1990; 30: 825-828.

51. German CL, Fleckenstein AE, Hanson GR. Bath salts and synthetic cathinones: An emerging designer drug phenomenon. Life Sci. 2014; 97: 2-8.

52. Fratantonio J. Designer Drugs: A Synthetic Catastrophe. J Reward Defic Syndr. 2015; 1: 82-86.

53. Freudenmann RW, Öxler F, Bernschneider-Reif S. The origin of MDMA (ecstasy) revisited: the true story reconstructed from the original documents. Addiction. 2006; 101: 1241-1245.

54. Zawilska JB, Wojcieszak J. Designer cathinones-An emerging class of novel recreational drugs. Forensic Sci Int. 2013; 231: 42-53.

55. Carroll FI, Lewin AH, Mascarella SW, Seltzman HH, Reddy PA. Designer drugs: a medicinal chemistry perspective. Ann N Y Acad Sci. 2012; 1248: 18-38.

56. Hill SL, Thomas SHL. Clinical toxicology of newer recreational drugs. Clin Toxicol. 2011; 49: 705-719.

57. Assessment of khat (Catha edulis Forsk). 2006.

58. Wood DM, Greene SL, Dargan PI. Clinical pattern of toxicity associated with the novel synthetic cathinone mephedrone. Emerg Med J. 2011; 28: 280-282.

59. Erowid MDPV (Bath Salts) Vault.

60. James D, Adams RD, Spears R, Cooper G, Lupton DJ, Thompson JP, et al. Clinical characteristics of mephedrone toxicity reported to the UK National Poisons Information Service. Emerg Med J. 2011; 28: 686-689.

61. Rivera JV, Vance EG, Rushton WF, Arnold JK. Novel Psychoactive Substances and Trends of Abuse. Crit Care Nurs Q. 2017; 40: 374-382.

62. Petrie M, Lynch KL, Ekins S, Chang JS, Goetz RJ, Wu AHB, et al. Cross-reactivity studies and predictive modeling of “Bath Salts” and other amphetamine-type stimulants with amphetamine screening immunoassays. Clin Toxicol. 2013; 51: 83-91.

63. Coppola M, Mondola R. Synthetic cathinones: Chemistry, pharmacology and toxicology of a new class of designer drugs of abuse marketed as “bath salts” or “plant food.” Toxicol Lett. 2012; 211: 144-149.

64. McCann UD, Wong DF, Yokoi F, Villemagne V, Dannals RF, Ricaurte GA. Reduced striatal dopamine transporter density in abstinent methamphetamine and methcathinone users: evidence from positron emission tomography studies with [11C]WIN-35,428. J Neurosci. 1998; 18: 8417-8422.

65. Prosser JM, Nelson LS. The Toxicology of Bath Salts: A Review of Synthetic Cathinones. J Med Toxicol. 2012; 8: 33-42.

66. Thakur GA, Nikas SP, Makriyannis A. CB1 Cannabinoid Receptor Ligands. Mini-Reviews Med Chem . 2005; 5: 631-640.

67. White CM. The Pharmacologic and Clinical Effects of Illicit Synthetic Cannabinoids. J Clin Pharmacol. 2017; 57: 297-304.

68. Cimanga K, Hermans N, Apers S, Van Miert S, Van den Heuvel H, Claeys M, et al. Complement-Inhibiting Iridoids from {<}i{>}Morinda{<}/i{>} {<}i{>}m{<}/i{>} {<}i{>}orindoides{<}/i{>}. J Nat Prod. 2003; 66: 97-102.

69. Dowling G, Regan L. A method for CP 47, 497 a synthetic non-traditional cannabinoid in human urine using liquid chromatography tandem mass spectrometry. J Chromatogr B. 2011; 879: 253-259.

70. Seely KA, Prather PL, James LP, Moran JH. Marijuana-based Drugs: Innovative Therapeutics or Designer Drugs of Abuse? Mol Interv. 2011; 11: 36-51.

71. Baumann MH, Solis E, Watterson LR, Marusich JA, Fantegrossi WE, Wiley JL. Baths Salts, Spice, and Related Designer Drugs: The Science Behind the Headlines. J Neurosci. 2014; 34: 15150-15158.

72. Seely KA, Lapoint J, Moran JH, Fattore L. Spice drugs are more than harmless herbal blends: a review of the pharmacology and toxicology of synthetic cannabinoids. 2012.

73. Rieder SA, Chauhan A, Singh U, Nagarkatti M, Nagarkatti P. Cannabinoid-induced apoptosis in immune cells as a pathway to immunosuppression. Immunobiology. 2010; 215: 598-605.

74. Every-Palmer S. Warning: Legal Synthetic Cannabinoid-Receptor Agonists Such As Jwh-018 May Precipitate Psychosis In Vulnerable Individuals. Addiction. 2010; 105: 1859-1860.

75. Benford DM, Caplan JP. Psychiatric Sequelae of Spice, K2, and Synthetic Cannabinoid Receptor Agonists. Psychosomatics. 2011; 52: 295.

76. Castellanos D, Thornton G. Synthetic Cannabinoid Use. J Psychiatr Pract. 2012; 18: 86-93.

77. The adverse health effects of synthetic cannabinoids. J Psychopharmacol. 2015; 29: 254–263.

78. Auwärter V, Dresen S, Weinmann W, Müller M, Pütz M, Ferreirós N. “Spice” and other herbal blends: harmless incense or cannabinoid designer drugs? J Mass Spectrom. 2009; 44: 832-837.

79. Mills B, Yepes A, Nugent K. Synthetic Cannabinoids. Am J Med Sci. 2015; 350: 59-62.

80. Armenian P, Vo KT, Barr-Walker J, Lynch KL. Fentanyl, fentanyl analogs and novel synthetic opioids: A comprehensive review. Neuropharmacology. 2017.

81. Lucyk SN, Nelson LS. Novel Synthetic Opioids: An Opioid Epidemic within an Opioid Epidemic. Ann Emerg Med. 2017; 69: 91-93.

82. Prekupec MP, Mansky PA, Baumann MH. Misuse of Novel Synthetic Opioids: A Deadly New Trend. J Addict Med. 2017; 11: 256–265.

83. Alzghari SK, Fleming SW, Rambaran KA, Long JE, Burkhart S, An J, et al. U-47700: An Emerging Threat. Cureus. 2017;

9: 3-6.

84. Bremer PT, Kimishima A, Schlosburg JE, Zhou B, Collins KC, Janda KD. Combatting Synthetic Designer Opioids: A Conjugate Vaccine Ablates Lethal Doses of Fentanyl Class Drugs. Angew Chemie-Int Ed. 2016; 55: 3772-3775.

85. Papsun D, Krywanczyk A, Vose JC, Bundock EA, Logan BK. Analysis of MT-45, a Novel Synthetic Opioid, in Human Whole Blood by LC–MS-MS and Its Identification in a Drug-Related Death. J Anal Toxicol. 2016; 40: 313-317.

86. Helander A, Bäckberg M, Beck O. MT-45, a new psychoactive substance associated with hearing loss and unconsciousness. Clin Toxicol. 2014; 52: 901-904.

87. Holstege CP, Borek HA. Toxidromes. Crit Care Clin. 2012; 28: 479-498.

88. Tenore PL. Advanced Urine Toxicology Testing. J Addict Dis. 2010; 29: 436-448.

89. Baumann MH, Pasternak GW. Novel Synthetic Opioids and Overdose Deaths: Tip of the Iceberg? Neuropsychopharmacology. 2018; 43: 216-217.

90. Araújo AM, Carvalho F, Bastos M de L, Guedes de Pinho P, Carvalho M. The hallucinogenic world of tryptamines: an updated review. Arch Toxicol. 2015; 89: 1151-1173.

91. Boland DM, Andollo W, Hime GW, Hearn WL. Fatality due to acute alpha-methyltryptamine intoxication. J Anal Toxicol. 2005; 29: 394-397.

92. Corkery JM, Durkin E, Elliott S, Schifano F, Ghodse AH. The recreational tryptamine 5-MeO-DALT (N,N-diallyl-5-methoxytryptamine): A brief review. Prog Neuro-Psychopharmacology Biol Psychiatry. 2012; 39: 259-262.

93. Brandt SD, Freeman S, McGagh P, Abdul-Halim N, Alder JF. An analytical perspective on favoured synthetic routes to the psychoactive tryptamines. J Pharm Biomed Anal. 2004; 36: 675-691.

94. Schmidt MM, Sharma A, Schifano F, Feinmann C. “Legal highs” on the net-Evaluation of UK-based Websites, products and product information. Forensic Sci Int. 2011; 206: 92-97.

95. Tittarelli R, Mannocchi G, Pantano F, Romolo FS. Recreational Use, Analysis and Toxicity of Tryptamines. Curr Neuropharmacol .2015; 13: 26-46.

96. Fantegrossi WE, Murnane KS, Reissig CJ. The behavioral pharmacology of hallucinogens. Biochem Pharmacol. 2008; 75: 17-33.

97. Fantegrossi WE, Murnane KS, Reissig CJ. The behavioral pharmacology of hallucinogens. Biochem Pharmacol. 2008; 75: 17-33.

98. Ray TS. Psychedelics and the Human Receptorome. Manzoni OJ, editor. PLoS One. 2010; 5: e9019.

99. Nagai F, Nonaka R, Satoh Hisashi Kamimura K. The effects of non-medically used psychoactive drugs on monoamine neurotransmission in rat brain. Eur J Pharmacol. 2007; 559: 132-137.

100. Alatrash G, Majhail NS, Pile JC. Rhabdomyolysis After Ingestion of “Foxy,” a Hallucinogenic Tryptamine Derivative. Mayo Clin Proc. 2006; 81: 550-551.

101. Brush DE, Bird SB, Boyer EW. Monoamine oxidase inhibitor poisoning resulting from Internet misinformation on illicit substances. J Toxicol Clin Toxicol. 2004; 42: 191-195.

102. Jovel A, Felthous A, Bhattacharyya A. Delirium Due to Intoxication from the Novel Synthetic Tryptamine 5-MeO-DALT. J Forensic Sci. 2014; 59: 844-846.

103. Muller AA. New Drugs of Abuse Update: Foxy Methoxy. J Emerg Nurs. 2004; 30: 507-508.

104. Itokawa M, Iwata K, Takahashi M, Sugihara GI, Sasaki T, Abe YI, et al. Acute confusional state after designer tryptamine abuse. Psychiatry Clin Neurosci. 2007; 61: 196-199.

105. Shulgin AT. The Background and Chemistry of MDMA. J Psychoactive Drugs. 1986; 18: 291-304.

106. Dean BV, Stellpflug SJ, Burnett AM, Engebretsen KM. 2C or Not 2C: Phenethylamine Designer Drug Review. J Med Toxicol. 2013; 9: 172-178.

107. Liechti M, Baumann C, Gamma A, Vollenweider FX. Acute Psychological Effects of 3,4-Methylenedioxymethamphetamine (MDMA, “Ecstasy”) are Attenuated by the Serotonin Uptake Inhibitor Citalopram. Neuropsychopharmacology. 2000; 22: 513-521.

108. Iravani MM, Asari D, Patel J, Wieczorek WJ, Kruk ZL. Direct effects of 3,4-methylenedioxymethamphetamine (MDMA) on serotonin or dopamine release and uptake in the caudate putamen, nucleus accumbens, substantia nigra pars reticulata, and the dorsal raphé nucleus slices. Synapse. 2000; 36: 275-285.

109. Office of Diversion Control D. 2,5-DIMETHOXY-4-(n)-PROPYLTHIOPHENETHYLAMINE (Street Names: 2C-T-7, Blue Mystic, T7, Beautiful, Tripstay, Tweety-Bird Mescaline). 2013.

110. Vilke GM, DeBard ML, Chan TC, Ho JD, Dawes DM, Hall C, et al. Excited Delirium Syndrome (ExDS): Defining Based on a Review of the Literature. J Emerg Med. 2012; 43: 897-905.

111. Meyer MR, Maurer HH. Metabolism of designer drugs of abuse: an updated review. Curr Drug Metab. 2010; 11: 468-482.

112. Vollenweider FX, Gamma A, Liechti M, Huber T. Psychological and Cardiovascular Effects and Short-Term Sequelae of MDMA (“Ecstasy”) in MDMA-Naïve Healthy Volunteers. Neuropsychopharmacology. 1998; 19: 241-251.

113. Sherlock K, Wolff K, Hay AW, Conner M. Analysis of illicit ecstasy tablets: implications for clinical management in the accident and emergency department. J Accid Emerg Med. 1999; 16: 194-197.

114. Boot BP, McGregor IS, Hall W. MDMA (Ecstasy) neurotoxicity: assessing and communicating the risks. Lancet. 2000; 355: 1818-1821.

115. Colado MI, Granados R, O’Shea E, Esteban B, Green AR. The acute effect in rats of 3,4-methylenedioxyethamphetamine (MDEA, "eve") on body temperature and long term degeneration of 5-HT neurones in brain: a comparison with MDMA ("ecstasy"). Phar-

macol Toxicol. 1999; 84: 261–266.

116. Parrott AC, Lasky J. Ecstasy (MDMA) effects upon mood and cognition: before, during and after a Saturday night dance. Psychopharmacology (Berl). 1998; 139: 261-268.

117. Kalant H. The pharmacology and toxicology of "ecstasy" (MDMA) and related drugs. CMAJ. 2001; 165: 917-928.

118. Schifano F. Potential Human Neurotoxicity of MDMA ("Ecstasy"): Subjective Self-Reports, Evidence from an Italian Drug Addiction Centre and Clinical Case Studies. Neuropsychobiology. 2000; 42: 25-33.

119. Spain D, Crilly J, Whyte I, Jenner L, Carr V, Baker A. Safety and effectiveness of high-dose midazolam for severe behavioural disturbance in an emergency department with suspected psychostimulant-affected patients. Emerg Med Australas . 2008; 20: 112-120.

120. Taylor RL, Maurer JI, Tinklenberg JR. Management of "bad trips" in an evolving drug scene. JAMA. 1970; 213: 422–425.