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Synthetic Drugs: A "Viral" Outbreak

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Abstract:

The term "synthetic drugs" is no longer a non-specific pharmacological phrase but one that describes a group of "designer drugs" which are responsible for global morbidity and mortality. In 2009, the United States (US) began experiencing the rapid emergence of these compounds and by 2010, cannabinoids (e.g. "K2," "spice") and cathinones (e.g. "bath salts," "flakka") had become known on the street as the new designer drugs of choice.

By definition, a "designer drug" is an analogue of a controlled substance which allows the user to experience the same, or similar, feelings as that from the controlled substance. With many derivitizations possible, new analogues may not be scheduled in the Controlled Substance Act (CSA). This permits the user to obtain a "legal high" with less fear of submitting a positive drug sample or other legal consequences. This is of paramount importance to our current synthetic drug abuse crisis as the Drug Enforcement Administration (DEA) is being inundated with new analogues at a rate faster than their ability to schedule these compounds within the CSA.

Synthetic drugs represent a considerable threat to the user as they may experience a desired euphoria, but with the risk of concomitant central nervous system (CNS) stimulation resulting in

tachycardia, hypertension, agitation, hyperthermia, seizures, rhabdomyolysis, excited delirium and violent behavior. Medical professionals attempting to treat these patients lack information regarding the chemical composition of these drugs and thereby can only offer symptom-based supportive care. However, treatment is often further hampered by the violent behavior manifested by these patients and protective actions needed by the medical team.

The synthetic drug abuse crisis reflects a number of similarities to a viral pandemic. The disease has spread rapidly throughout multiple countries via the assistance of a global carrier (the internet), with the virus mutation (analogue production) occurring at a pace that makes it difficult for agencies to quickly identify and regulate. Therefore, as in any disease outbreak, it becomes imperative for healthcare providers, scientists and law enforcement agencies to foster a mutual relationship of information exchange. Establishing an international database containing chemical structures of synthetic drugs, and their analogues, would allow for more prompt identification and regulation by policy makers looking to deter synthetic drug abuse worldwide.

Keywords:

Cannabinoids, Cathinones, Bath Salts, Flakka, K2, Spice, Serotonin, Dopamine, Norepinephrine, NPS, Excited Delirium, Analogues

Overview:

The term “synthetic drugs” is no longer a non-specific pharmacological phrase but one that describes a group of “designer drugs” which are responsible for global morbidity and mortality.[1] In 2009, the United States (US) began experiencing the rapid emergence of these compounds and

by 2010, cannabinoids such as “K2” and “spice,” and cathinones by the names of “bath salts” and “flakka,” had become known on the street as the new designer drugs of choice.

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Epidemiology:

In 2009, trending of synthetic drug abuse was first recognized by a noted increased in calls to poison control centers throughout the US.[4] Emergency department (ED) visits, from synthetic cannabinoids alone, rose from 11,406 visits in 2010 to 28,531 incidents in 2011.[5] The widespread popularity of these drugs can be attributed to a number of factors:

1) The lack of legal ramifications associated with these drugs has manufacturers promoting them as “legal highs.” This term may also portray the product as having a higher safety profile in comparison to an illicit drug bought off the street.[6] These drugs are packaged in a manner which is attractive to younger users and, with no purchasing age restriction, are easily accessible.[7,8]

2) Accessibility through the internet as well as widespread availability at local retailers including head shops, gas stations and convenience stores.[9] The use of synthetic drugs is

more prevalent among males, 25-29 years old, but ages range between teens and 40 years.[10,11] Users are typically single and have lower income and education levels.[12,13]

In order to determine the scope of any public healthcare epidemic, data from hospitals, medical examiners, the Centers for Disease Control (CDC), law enforcement and other entities must be considered. The underestimation of synthetic drug abuse is entirely possible due to our lack of adequate testing capabilities. Drug testing devices, within hospital laboratories, are generally not equipped with the degree of sophistication necessary to identify synthetic analogues. And, without laboratory confirmation of an illicit drug, the healthcare professional may simply list a diagnosis code based upon clinical presentation such as “altered level of mentation.”

The forensic crime laboratory has access to the equipment capable of identifying synthetic analogues. However, even medical examiners and toxicologists agree that their ability to make positive identification of all analogues is suspect. One of the most noteworthy cases of suspected synthetic drug abuse involved a Miami man who was attacked on May 26, 2012 by a perpetrator allegedly under the influence of “bath salts.” The perpetrator was killed when officers were unable to disengage him from attempting to “eat the face” of the victim. Subsequently, the Miami Dade Medical Examiner reported that “bath salts” were not detected in the perpetrator’s toxicology results. However, as commented upon by Dr. Bruce Goldberger, "There are many of these synthetic drugs that we currently don't have the methodology to test on, and that is not the fault of the toxicology lab. The challenge today for the toxicology lab is to stay on top of these new chemicals and develop methodologies for them but it's very difficult and very expensive. There is no one test or combination of tests that can detect every possible substance out there."[14]

A challenge for law enforcement agencies is the lack of field testing kits, specific to synthetic drugs, as available for other illicit substances such as cocaine.[15,16] Reliable field testing capabilities could also enhance efficiency by minimizing samples being forwarded to regional crime laboratories. This represents another scenario where underestimation of synthetic drug abuse might occur. Without reliable drug identification, the subject may be booked with an ancillary charge such as "disorderly conduct."

Clinical Management Considerations:

Synthetic drugs represent a considerable threat to the user as they may experience a desired euphoria, but with the risk of concomitant central nervous system (CNS) stimulation resulting in tachycardia, hypertension, agitation, hyperthermia, excited delirium, violent behavior and potentially death. Medical professionals attempting to treat these patients are often hampered by the patient's aggressive behavior and need for personal protective measures.[17]

Clandestine laboratories often divert clinical research so as to identify compounds which produce psychoactive effects. Concerns regarding the lack of quality control during clandestine synthesis, coupled with a lack of knowledge regarding the chemical structure of the ingested drug, places medical professionals at a disadvantage with regard to appropriate treatment.[18] Clinical laboratories, such as those found in hospitals, will generally not maintain equipment necessary to make positive identification of these types of analogues. Submitting samples to a forensic laboratory is cost prohibitive and not logistical if being used to treat a patient in an emergency setting. Oftentimes, even forensic laboratories are unable to provide an exact classification should the analogue structure not be listed within the major identification databases.[19]

Without being able to identify the specific pharmacologic agents involved, it is difficult to anticipate potential toxidromes. Presentations can vary significantly from mild irritability and central nervous system (CNS) stimulation to profound organ failure and death. With little medical training being afforded on the recognition and management of clinical scenarios involving these drugs, and no specific antidotes, staff members must rely simply on supportive care, often with benzodiazepines, for specific symptomology.

Regulatory Efforts:

A literature review confirms that a global effort is underway to reduce synthetic drug abuse. Numerous countries are reporting encounters with these synthetic drugs. The amount of abuse varies with each country and is largely dependent on their current regulations.[20] Altering the chemical structure of synthetic drugs, through substitutions or variances of the side chains, can produce a separate analogue which is not recognized as being illicit. Therefore, databases can differ from country to country as to what is considered illicit. Identification can also be impacted by chemicals, used as precursors for the synthesis of the new analogues, which reinforces the need to regulate these compounds.

Subsequent to the influx of synthetic drugs in 2007, the European Union originated the term “new psychoactive substances” (NPS) to describe a narcotic or psychoactive drug not currently scheduled under either the Single Convention on Narcotic Drugs of 1961 or the Convention on Psychotropic Substances of 1971, but considered to be a potential threat to the public health.[21]

In the United States, the Drug Enforcement Administration (DEA) is tasked with the determination of whether a drug represents a threat to public health and, if so, takes steps to schedule the drug accordingly. Under the CSA, substances can be classified into five separate divisions known as "schedules." Schedule I represents the most dangerous of drugs and includes drugs, substances, or chemicals with no currently-accepted medical use, great potential for severe physiological and/or psychological dependence and a high potential for abuse.[22]

Because of concerns by policy makers regarding "pharmaceutically created and other modified drugs," the Attorney General, in conjunction with the DEA, was given authority in 1984 to "temporarily place a substance onto Schedule I of the CSA" if it was deemed that an imminent threat existed to public health.[23] In 2011, sequellae from the influx of synthetic analogues was deemed to represent such a threat, at which time the Attorney General exercised his authority and ordered an emergency placement of five synthetic cannabinoids, and three synthetic stimulants, on Schedule I of the CSA.

Once a drug has been named to Schedule 1 through this temporary process, it may remain there for a period of two years. If deemed necessary, the Attorney General may extend that time for one additional one year. At the terminus of that additional year, the drug is then permanently scheduled or removed.

In 2012, pursuant to the Synthetic Drug Abuse Prevention Act of 2012—Subtitle D of Title XI of the Food and Drug Administration Safety and Innovation Act (P.L. 112-144), five structural

classes of substances known to be synthetic cannabinoids and their analogues, as well as eleven synthetic stimulants, were placed on Schedule 1 of the CSA.

In 2013, methylone was permanently placed on Schedule 1 of the CSA and in March of 2014, ten synthetic cathinones were added on to Schedule 1 of the CSA.[24]

The CSA was amended through the Controlled Substances Analogue Enforcement Act of 1986, to include analogues of controlled substances "intended for human consumption" as a controlled substance under Schedule 1. Under this law, an analogue is considered a drug with a similar chemical structure and physical effects as a drug currently classified under Schedule 1. Law enforcement and regulatory agencies encounter numerous obstacles in attempting to deter the abuse, as suppliers will provide disclaimers on the product packages, stating that the content is "not for human consumption" in order to avoid regulation.[25] Additionally, regulatory efforts may be hampered due to the fact that chemical structures of certain analogues may be similar to the chemical structures of licit drugs. One example is that of MDPV (3,4-methylenedioxypyrovalerone) and its similarity to certain anti-depressants and treatments for aphylaxis.[26]

Since the scheduling of mephedrone (4-methyl-N-methylcathinone), methylone (4-methylenedioxy-N-methylcathinone) and MDPV, the number of reports received by the American Association of Poison Center has decreased from 2,676 in 2012 to 690 through August of 2013.[27]

Monitoring:

Another tool through which regulatory entities may receive assistance is that of monitoring. Whenever a threat to public health is incurred, various entities are critical to evaluating the scope of that threat and monitoring progress. Some of the following entities should be considered:

- Government agencies such as SAMHSA (Substance Abuse and Mental Health Services Administration) provide various reports that monitor public health threats. The DAWN (Drug Abuse Warning Network) is one of SAMHSA's surveillance systems monitoring emergency department visits related to drug abuse. The N-SSATS (National Survey on Substance Abuse Treatment Services) reflects information from both public and private substance abuse treatment facilities. The N-MHSS (National Mental Health Services Survey) provides information from public and private mental health treatment facilities. The TEDS (Treatment Episode Data Set) provides demographic characteristics, as it relates to substance abuse, from treatment facilities. The NSDUH (National Survey on Drug Use and Health) survey provides epidemiologic information on prevalence, consequences and patterns of illegal drug in the general population ages 12 and older.

- Poison centers across the country can be a valuable source of data as callers do not fear legal ramifications. Specific information, such as street names, may be obtained as well as physical descriptions of the drug and associated paraphernalia.

- Information gained from forensic analysis is another avenue of monitoring the prevalence of synthetic drug abuse. Samples may be obtained from law enforcement seizures or during post-mortem examination. Forensic analysis provides valuable information as the

scientist involved is privy to a level of testing, such as gas chromatography-mass spectrometry (GC/MS), which can provide positive identification of many known synthetic drug structures. Forensic scientists utilize database "libraries" of chemical structures and these "libraries" are growing as additional synthetic drugs, and their analogues, are identified and added. The difficulty arises with compounds which contain ingredients not yet identified; therefore no reference substance exists that can be used for comparison and verification. However, this level of technology is expensive and funding may not be available for certain laboratories in the US or other affected countries.

- Attempts to obtain data through prospective or retrospective surveys can be time consuming in light of the need for institutional review board (IRB) approval processes as well as survey tool development, evaluation and analysis. With the drug branding continually undergoing change, as well as varying availability of the drugs, the results of these surveys may be outdated by the time of publication.

- Although the internet has become a global "carrier" in the synthetic drug abuse pandemic, it can also be utilized for monitoring along with open source information sites such as forums and chat rooms.[28] Challenges faced by those using this tool are common to those regulating synthetic drug abuse in general, namely the constant influx of new compounds being introduced. Marketers of these drugs use an assortment of brand names, many of which appear innocuous to the user. This is in conjunction with the marketing strategy of those providing "legal highs" specifically to promote an attitude of

safety, both physically and from legal ramifications. Additionally, these product names are transient oftentimes due to regulatory sanctions.

Synthetic Cannabinoids

Overview:

Synthetic cannabinoids represent a wide array of compounds which were produced in order to mimic the chemical effects of tetrahydrocannabinol (THC) - the active chemical in marijuana.[29] Once synthesized, these compounds can be sprayed on to plant material or herbs and then marketed as seemingly innocuous items such as potpourri or incense. These drugs can be administered orally, intranasally or by inhalation. Common “street” names include, but are not limited to, Spice Gold, Spice Diamond, Purple Haze, K2, Skunk, and Smoke.

History:

Although our current cannabinoid epidemic has evolved since 2009, the origin of synthetic cannabinoids may well have occurred greater than twenty years ago. Scientists at Sterling-Winthrop were researching a drug by the name of Pravadoline which was being considered as an non-opioid analgesic lacking cyclooxygenase inhibition.[30] The drug was later discovered to be nephrotoxic and an aminoalkylindole analogue was developed to determine the mechanism of action causing this toxicity.[31,32] WIN 55,212-2 was discovered through this process and proved to be a fairly potent analgesic however, the manufacturers discontinued its synthesis after discovering that WIN 55,212-2 and its analogues were cannabimimetic.[33,34]

In 1988, Devane et al reported the identification of the cannabinoid receptor - CB_1 - and research continued with respect to binding properties of cannabinoids. Subsequent to this research, it was determined that, in addition to WIN55,212-2, other compounds such as CP55,940 and anandamide demonstrated cannabinoid agonistic properties.[35,36]

It was from the work of a former Clemson professor, John W. Huffman (JWH), that synthetic cannabinoids were introduced, and subsequently embraced, by those seeking to exploit these drugs for illicit purposes.[37] Dr. Huffman's research on the cannabinoid system resulted in the synthesis of a number of indole-derived cannabinoids, including JWH-018, which was one of the first to be identified by forensic toxicologists as an evolving drug of abuse. The cannabinoid was being sprayed on plant material, such as incense, and then smoked to experience manifestations similar to marijuana.[38]

The following is a list which includes, but is not limited to, some of the more common synthetic cannabinoids:

- JWH-018
- JWH-122,
- JWH-210
- AM2201,
- XLR11
- FDU-PB-22
- FDU-NNEI
- AB-CHMINACA

- NNEI

Pharmacology:

Delta-9-tetra-hydrocannabinol (THC), the primary cannabinoid in marijuana, demonstrates a partial agonistic effect at the CB_1 receptor. This receptor, though located throughout the body, is predominantly found in the CNS. The psychoactive effects from synthetic cannabinoids occur subsequent to stimulation of the endocannabinoid system including both the CB_1 receptors in the brain and CB_2 receptors in the periphery. In addition, anandamide and 2-arachidonoyl glycerol (endogenous ligands) and metabolic enzymes are involved in metabolism.

Metabolites from synthetic cannabinoids, unlike those from Δ^9-THC, may retain biologic activity and continue to act as agonists at CB_1 receptors.[39] Duration of symptoms is variable with reports of 1-2 hours as well as 6-8 hours depending upon the specific cannabinoid. Due to a stronger affinity for the CB_1 receptor than marijuana, abuse of the synthetic cannabinoids is associated with a greater euphoric effect. However, studies reveal that there is also a greater CNS response including tachycardia, tachypnea, hypertension, seizures, rhabdomyolysis and hallucinations. This may be partly attributed to common adulterants such as the β2–adrenergic agonist clenbuterol.

Synthetic Cathinones

History:

“Bath salts” have been prevalent in Europe since 2007 but did not appear in the US until the end of 2010. The drug gained popularity in the recreational drug arena during 2011 as was

demonstrated by a sharp rise in emergency department (ED) visits for synthetic drug toxicity.[40] From 2010 to 2011, the number of calls to poison centers involving “bath salts” rose from 304 to 6138.[41]

The name “bath salts” was derived from the appearance of one of the first analogues. As a white crystalline powder, the analogue appeared similar to licit bath salts or Epsom salts and thereby inferred it to be a harmless substance. The powder is also portrayed as plant food or household cleaners and, in order to circumvent regulatory controls, many of the packages include the disclaimer “not for human consumption.”[42] “Bath salts” are sold through internet sources, local head/smoke shops, adult books stores and gas stations.

Cathinones can be administered intranasally but can also be ingested orally, intravenously or intramuscularly. The analogue mephedrone is not suitable for smoking. Additional names of “bath salts” include, but are not limited to, “Ivory Wave,” “Vanilla Sky,” “Energy 1,” “Explosion,” “Meow Meow,” “Bubbles,” "Purple Wave," "Zoom," and "Cloud Nine."

Pharmacology:

Analysis of “bath salts” products commonly reveals the presence of three predominant main synthetic cathinones:[43]

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

As these drugs are products of clandestine laboratories, the chemicals being produced can vary in structure and may also contain pyrovalerone or pipradrol derivatives.[44] In the US, MDPV is more commonly found as opposed to European countries where mephedrone appears to be more popular.[45]

The synthetic cathinones belong to a family of stimulants including amphetamine, methamphetamine, 3,4 methylenedioxymethamphetamine. They are structurally related to a naturally occurring form of cathinone which is found in the flowering shrub Khat (*Catha edulis*). Khat, which is endemic to East Africa and the Arabian-Peninsula, has been used as a recreational drug since the 13th century[44] and is popular among Somalian and Ethiopian communities within the US.[45] As cathinone is a β-ketone amphetamine, the user can experience the euphoric and stimulatory effects by chewing the Khat leaves.[47]

Cathinones act by increasing the extracellular levels of monamine neurotransmitters (i.e. serotonin [5-HT], dopamine [DA] and norepinephrine [NE]) through facilitation of extracellular release as well as reuptake inhibition.[48] Specifically, MDPV serves as a reuptake inhibitor of DA and NE, with little effect on 5-HT, at a potency ten times greater than that of cocaine. Methylone and mephedrone facilitate monoamine release and mimic the effects of 3,4-methylenedioxymethamphetamine (MDMA).[49] Although cathinones share chemical structure similarities, their neuropharmacological profiles are individual and result in a variety of manifestations (e.g. hyperthermia, anxiety and musculoskeletal coordination).[50]

Physiologic effects are noted within 10-20 minutes after administration, often peak at 45-90 minutes for and then decrease over the next 6-12 hours. Multiple doses may be consumed during a session in order to prolong the desired effects.[51,52] Clinical manifestations are sympathomimetic in nature and include tachycardia, hypertension, tachypnea, hyperthermia, heightened sense of alertness and potential for aggressive behavior.

Another member of the cathinone family, α-Pyrrolidinopentiophenone (α-PVP), has been gaining in popularity. As with other cathinones, the mechanism of action involves inhibition of neurotransmitter reuptake, specifically DA, in the case of α-PVP.[53]

Additional names for this particular cathinone include:

- alpha-Pyrrolidinovalerophenone
- α-PVP
- alpha-PVP
- O-2387
- β-keto-prolintane
- Prolintanone
- Desmethyl Pyrovalerone

The street names for α-PVP are regional. In Florida, the term “flakka” is associated with α-PVP whereas this drug is referred to as “gravel” in other areas of the country. This analogue was listed as a Schedule 1 drug on January 28, 2014.

Conclusions:

The synthetic drug abuse “pandemic” represents a significant public health threat as demonstrated through increased emergency department visits, poison center data and acts of violence reported by law enforcement agencies. There are a number of similarities between the threat represented by synthetic drug abuse and other virus-based pandemics:

- The “virus” has spread rapidly with assistance of a global carrier – the internet.
- The morbidity and mortality have been significant, as indicated through the Centers for Disease Control and other public health related entities.
- The “virus” continues to mutate subsequent to substitutions and variances.
- The rate of replication is occurring at such a rapid rate that identification and regulation is difficult to achieve as quickly as needed.

Identifying the etiology of any disease is paramount to the ability to provide treatment. As indicated throughout the body of this article, one of the greatest obstacles facing healthcare and regulatory entities is the ability to identify the growing number of synthetic drugs, and their respective analogues, which are responsible for morbidity and mortality. The development of an international database or “library”, containing information on the various chemical structures of cannabinoids and cathinones, could serve to assist in identification and subsequent regulatory measures. Healthcare providers, scientists and law enforcement agencies must foster a mutual relationship of information exchange in order to more appropriately evaluate the scope of this threat and define policies aimed at treatment and prevention.

Conflict Of Interest

I declare that I have no proprietary, financial, professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled: *"Synthetic Drugs: A "Viral" Outbreak"*.

About the Author

Dr. Sharon Kelley serves as the CEO for the Associates in Emergency Medical Education and the Alliance for Global Narcotics Training. While completing her Bachelors in Pre-Medical Sciences she served as a Tampa police officer which afforded her firsthand experience in recognition of street and prescription drug abuse. She received a Master's Degree in Drug Chemistry from the University of Florida and then obtained her PhD in Toxicology. She serves as an affiliate faculty member for the University Of South Florida College Of Medicine and as a narcotics consultant for the Florida Attorney General, Department of Health, Veteran's Court and numerous law enforcement entities. She lectures nationally and internationally to medical, legal and corporate entities, including military and sports organizations, to enhance their medical/legal management of licit and illicit drug abuse.

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