Designer Drugs: An Escalating Public Health Challenge

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Abstract

Designer drugs are created to be similar to, but not identical with psychoactive drugs that are illegal to possess or sell for human consumption. A recurring threat to public health, the designer drug sub-culture has exploded over the past decade. The rapid expansion can be attributed to a convergence of key technological advances combined with devious, aggressive marketing schemes. Globally accessible internet sites provide detailed information on the sensations produced by newly created drugs, how to synthesize them, and easy venues for buying the "research chemicals", "bath salts", "plant foods", "incense", and "plants" from websites. Frequently, these sites are impervious to legal sanctions, as it takes time to deliberate the evidence and move newly emerging drugs into a legally restrictive zone. This challenge is compounded by imperfect international agreements and a gradual dissolution of international resolve for combating drug use with supply side restrictions and laws. The designer drug industry is a niche business with a simple strategy to: (a) circumvent existing drug laws and promote their "products" as legal, (b) create new markets with rapid profits, (c) undercut producers and prices of common illegal drugs (e.g. cocaine, marijuana, and heroin), and (d) undermine routine clinical drug

testing. The consumer misperceives the drugs as legal, less hazardous than conventional street drugs, and more intriguing. They are more challenging to detect and easier to evade routine clinical drug testing. This overview summarizes legal, biological and psychoactive effects of two classes of designer drugs, cathinone-based psychostimulants packaged as "bath salts" and synthetic cannabinoids sold as "Spice" or "K2". The essay concludes with a set of policy recommendations.

A.   Introduction

Over millennia, humans serendipitously discovered that certain ingested plants were a source of unique rewarding sensations, beyond satiety. Some were mildly arousing (e.g. nicotine, caffeine), others enhanced mood or altered perception, reduced pain, intoxicated, or produced euphoria (e.g. alcohol, marijuana, hallucinogens, opiates, cocaine). In the past two centuries, consumption of these psychoactive substances expanded rapidly. Purification of the active chemicals, delivery by devices for maximum effect and global marketing contributed to this expansion. Modern chemistry has produced a vast array of variations of these plant products, paralleled by an unprecedented level of adverse biological, behavioral, medical and social consequences.

Designer drugs are created to be similar to, but not identical with psychoactive drugs that are illegal to possess or sell for human consumption - unless for medical purposes. It attracts those seeking "legal highs" and reflects the view that designating a drug as illegal attenuates use.

A recurring threat to public health, the designer drug sub-culture has exploded over the past decade. The rapid expansion can be attributed to a convergence of key technological advances combined with devious, aggressive marketing schemes. Globally accessible internet sites provide detailed information on the sensations produced by newly created drugs, how to synthesize them, and easy venues for buying the "research chemicals", and "bath salts", from websites. These sites are frequently impervious to legal sanctions, as it takes time to deliberate the evidence and move newly emerging drugs into a legally restrictive zone. This challenge is compounded by

imperfect international agreements, and a gradual dissolution of international resolve for combating drug use with supply side restrictions and laws.

A blunt snapshot of the global reach of this market can be gleaned from the European Union funded Psychonaut Web Mapping Project aimed at real-time identification of emerging new psychoactive substances ("legal highs") through regular monitoring of the Internet: over 200 discussion forums, social media, online shops, websites and other Internet resources through YouTube, eBay, Google, and Google Insight (1). From these sites, more than 410 substances/products were recorded (121 herbal compounds, 153 chemical compounds, and 140 combinations). Not all became catalysts for a public health response and not all fell under the "illegal umbrella". Detailed, valuable information emerged from these websites and forums, especially for substances with limited or nonexistent scientific publications. The rise of "Spice", mephedrone, naphyrone, MDAI (5, 6-methylenedioxy-2-aminoindane), and MDPV (methylendioxypyrovalerone) were tracked from single source countries until they spread widely. After they fell into the illegal zone of control, online searches decreased (1). This study dramatically highlights the cost-benefit of the internet, as a hub of information on designer drugs for consumers, but also as a propitious source of market trends for public health and law enforcement officials.

1. What are designer drugs?

Designer drugs are produced in laboratories, the majority resembling drugs legally restricted for distribution and possession. They share one common trait, producing psychoactive effects that can range from cannabis-like, psychomotor stimulation, dissociative anesthesia to hallucinogenic. Examples include mephedrone, methylone, MDPV, ethylphenidate, synthetic cannabinoids in "Spice" or "K2", 2,5-dimethoxy-4-(n)-propylphenethylamine (2C-P), N-adamantyl-1-pentylindole-3-carboxamide (2NE1), methiopropamine, and methoxetamine. They are sold inexpensively as bulk powders, and are deceptively labeled "research chemicals", "bath salts", plant food" "incense", "food", or by other names and designated "not for human consumption". The designer drug industry is a niche business with a simple strategy to: (a) circumvent existing drug laws and promote their "products" as legal, (b) create new markets with rapid profits, (c) undercut producers and prices of common illegal drugs (e.g.

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cocaine, marijuana, and heroin), and (d) undermine routine clinical drug testing. The consumer misperceives the drugs as legal, less hazardous than conventional street drugs and more intriguing. They are more challenging to detect and easier to evade routine clinical drug testing. Standard strip tests do not identify most of these compounds. Nonetheless, most drugs or their metabolites are effortlessly isolated from biological samples, including hair samples, and can be identified in laboratories with standard or advanced analytical techniques (2, 3).

2. Sources and complexity

The range of substances available is wider than ever before, with the internet enabling a global marketing stream of choice and access. Primary sources are unregulated laboratories in Asia. For example, manufacturers in various cities in China (Wuhan, Changzhou, Shanghai, Hangzhou, Beijing) directly market a variety of designer drugs on the internet as "research products" or chemicals, "not for human consumption", which can be allocated and sold in innocuous–looking packets. Designer drugs may evoke psychoactive effects similar to the parent drug, or elicit a more intense, amplified, unique or life-threatening response. Some are designed to mimic Schedule I or lower schedule drugs (e.g. THC or tetrahydrocannabinol, cocaine, cathinone, amphetamine, or methamphetamine, ketamine, LSD or lysergic acid diethylamide, methaqualone), while others create complex sensations because of their hybrid structures, and amalgamation of substances. Infrequently, new drugs are designed or discovered that have neither precedent in medicinal chemistry nor a long history of abuse (e.g. SalvinorinA), yet may possess equal or greater abuse potential or health hazards.

With the exception of barbiturates and benzodiazepines, psychoactive pharmaceuticals originated largely as modified plant products (e.g. ephedrine, THC, ergot, cocaine, morphine, cathinone). Designed by medicinal chemists in pharmaceutical companies, universities and small research companies for medications development, the vast majority were rejected because of their poor therapeutic potential, based on safety and efficacy trials. Others were created for basic research, to clarify the biological targets of plant products or to investigate mechanisms of chemical communication in the brain. For example, synthetic cannabinoids were instrumental in

mapping the targets of marijuana in the brain. The brain regions expressing marijuana sites of action were consistent with its array of psychoactive properties. The hippocampus, a brain region essential for learning and memory, harbored high concentrations of cannabinoid signaling receptors. Analogs of cocaine are another example of chemical modifications created for biological research. A radioactive analog of cocaine clarified the biological targets of cocaine in the brain (4). After being shelved in research laboratories, in dormant patents, or medicinal chemistry journals, these compounds are being revived as "designer drugs" by chemists (5). The majority of designer drugs are concocted by changing or inserting a few or more atoms into the core structures of legal or illegal drugs, by mining old sources (chemical journals, patents), or by creating new entities based on existing structures. Although these modifications can drastically transform the psychobiology of the parent drug, a slight or major structural variation can temporarily evade legal definitions, penalties and consequences. By this strategy, designer drugs are manipulated into a legal "grey zone".

A challenge to the scientific and the consumer community is the complexity of unregulated production of these chemicals. Laboratory analyses of 124 different "K2" cannabinoids products and other "bath salts" submitted to the Arkansas Designer Drug Research Consortium identified the inclusion of over 240 distinct chemicals in 46 different combinations of compounds, including the cathinones MDPV, 4-methylmethcathinone (methylone, 4-MMC), 3,4-methylenedioxymethcathinone (mephedrone), as well as caffeine, lidocaine, methamphetamine, levamisole, benzocaine, and synthetic cannabinoids (Dr. JH Moran, Arkansas Dept of Health, reported at the annual CPDD meeting, June 2012). Without quality assurance and deceptive labeling practices, compounds vary from product to product, from batch to batch and even contain "hot spots" within each packet. This array of untested poly-pharmaceuticals place users at great risk to their health, baffle emergency department physicians, and render the medical community defenseless in identifying the most significant threat to patients' health and selecting effective antidotes.

B.   Legal History and Status

Drug traffickers circumvented drug laws by developing analogs of banned opioids as early as the 1920's. During the 1960's a rash of new psychoactive drugs were introduced to American culture. The movement to normalize use and the resulting pandemonium catalyzed the formation of the Drug Enforcement Administration (DEA) in the United States in 1973, establishing a single unified federal agency to regulate drugs with high abuse potential. The resistance to drugs and a shift in perceptions took years to penetrate public opinion, when drug use became viewed as reducing natural potential, and the consequences of drugs in family members, schools, and the workplace, begin to take a toll. Drugs were placed into 5 categories known as schedules. Schedule I substances have a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use of the drug under medical supervision. These drugs include. heroin, lysergic acid diethylamide (LSD), marijuana (cannabis), peyote, methaqualone, and MDMA or ecstasy. Legal psychoactive drugs classified as Schedule II drugs have accepted medical use, and a high potential for abuse which may lead to severe psychological or physical dependence. Examples of these drugs are opioids (methadone, oxycodone, hydromorphone, meperidine, fentanyl), stimulants (cocaine, amphetamine, methamphetamine, methylphenidate), and barbiturates; Drugs in Schedule III (hydrocodone, buprenorphine, codeine, ketamine and anabolic steroids), Schedule IV (propoxyphene, benzodiazepines), and Schedule V (low dose narcotics for cough, diarrhea, or pain) have decreasing abuse liability, but accepted medical uses. Encroachment of regulations by non-medical use of scheduled drugs reflects a growing challenge to the medical and law enforcement community. Prescription medications, primarily opioid analgesics, may be legally obtained by a single physician, by "doctor-shopping" (obtaining multiple prescriptions from multiple physicians, even crossing state lines to accumulate supplies), from friends and family (without payment) and used inappropriately by intended or unintended persons for psychoactive purposes or chemical coping. Marijuana can be "recommended", but not prescribed by a physician in states that have approved its use, even though it is not approved by the Food and Drug Administration (FDA) and remains an illegal drug, classified in Schedule I by the Federal government. The majority of designer drugs are similar in chemical structure to illegal or legal drugs currently under federal and/or international control. Emergency scheduling has inserted a number of them into Schedule I, on the basis of accumulating evidence that they are health hazards.

Advocates of stringent legal restrictions and policies for drugs view drug issues through a prism of concerns for human health, welfare, social and safety. The DEA has drawn legal distinctions among substances, but these boundaries are frequently breached by substance abusers. Law enforcement is in a perpetual race to outflank designer drug producers and dealers. As the federal government cannot prosecute until drugs are marketed, the Comprehensive Crime Control Act of 1984 amended the Controlled Substances Act (CSA) to allow the DEA Administrator to temporarily schedule an abused, harmful, non-medical substance in order to avoid an imminent hazard to public safety while the formal rule-making procedures are in process. This change required that a controlled substance be a single chemical of known structure, but this criterion could be circumvented readily by slight chemical modifications. Regulation of new "designer drugs" was catalyzed by the reported deaths from consumption of 4-methylfentanyl or "China White", an opioid approximately 30 times more potent than the extremely potent fentanyl (6). In response, Congress enacted the Controlled Substance Analogue Enforcement Act of 1986, which defined a "controlled substance analogue" as a chemical structure "substantially similar" to the chemical structure of a controlled substance in schedule I or II, with psychoactive properties (i.e. stimulant, depressant, hallucinogen), similar to the controlled substance in Schedule I or II.   Yet, the "substantially similar" clause proved to be ineffective in protecting the public, with the appearance of synthetic cannabinoids which are structurally quite distinct from THC or Δ9-tetrahydrocannabinol yet engendering similar psychoactive effects (6).

In 2011, the Synthetic Drug Control Act (H.R. 1254) amended the earlier CSA with a new provision to schedule "cannabimimetic agents," as functional compounds that act at the cannabinoid receptor1 (CB1). With this strategy, the Act attempted to preempt distribution of new molecules, regardless of structure, that would have the same end point - a pharmacological response similar to THC at the cannabinoid receptor1. The law also incorporated new restrictions on substituted cathinones and hallucinogenic phenethylamines, anticipating that the chemistry literature would be excavated to identify and circumvent weaknesses inherent in the "controlled

substance analogue" law. The net effect is to raise the barriers to "legal highs" and expand the "red zone" of federal law by anticipating a broader range of chemicals that can be abused, by adding psychoactive properties *and* biological targets (e.g. receptors) as criteria for scheduling a compound.

As of 2012, the DEA currently has emergency powers to temporarily schedule a drug for 36 months, a much longer time period to accumulate enough evidence to deposit the drug permanently in a "red zone". When poison control centers, physicians' offices, emergency rooms or morgues, become flooded with designer drug crises, the legal "grey zone" can now rapidly morph into an illegal "red legal" zone. In October 2011, the United States Drug Enforcement Agency (DEA) asserted itself and brought the full weight of the federal government to controlling distribution of newly emerging designer drugs. Exercising its emergency scheduling authority, the DEA controlled three synthetic stimulants (mephedrone, 3, 4-methylenedioxypyrovalerone (MDPV) and methylone) that had been marketed as "bath salts" and "plant food". Specific health crises related to synthetic marijuana also aroused a rapid DEA response (7). The American Association of Poison Control Centers reported that they received 6,959 calls related to synthetic marijuana in 2011, up from 2,906 in 2010 (8). On March 1 2012, the DEA extended, by six months, control of five chemicals that are designed as "fake marijuana" products (JWH-018, JWH-073, JWH-200, CP-47,497, cannabicyclohexanol. In June 2012, 26 synthetic drugs, including 15 different synthetic cannabinoids, were placed under the Controlled Substance Act. These actions made possession and sale of these chemicals, or the products that contain them, illegal in the United States. The DEA deemed the emergency actions necessary to prevent an imminent threat to the public safety. The temporary scheduling action on specific compounds will remain in effect for one to three years while the DEA and the United States Department of Health and Human Services (DHHS) further study whether these chemicals should be permanently controlled.

The DEA is not the only government agency responding to an increasing number of reports from poison control centers, hospitals and law enforcement regarding products containing one or more of these chemicals. More than

43 states and the US Armed Forces have taken action to control or ban these or other synthetic stimulants, with counties and municipalities also using local ordinances to restrict distribution. The long-term physical and psychological effects of these products are unknown, but potentially severe. They have become increasingly popular, targeting our most promising and yet vulnerable populations - teens and young adults. They are sold at a variety of retail outlets, in head shops and over the Internet. Without approval by the Food and Drug Administration for human consumption or for medical use, there is no oversight of the manufacturing process, safety, purity or other standards routinely imposed by the FDA. DEA Administrator Michele M. Leonhart has stated that, "These chemicals pose a direct and significant threat, regardless of how they are marketed, and we will aggressively pursue those who attempt their manufacture and sale."

2. *Rationale for Legal Restrictions*

Opinions vary widely on how nations should respond to drug threats and challenges to public health. Some nations have moved to categorize drugs in terms of their potential harm, with the possibility of deregulating designer drugs that, in some opinions, are deemed safe. Some individuals have claimed that designer drugs are an appalling response to, and an unintended adverse consequence of, regulating conventional psychoactive street drugs (e.g. marijuana, cocaine, LSD). By designating conventional drugs as illegal, they claim a more dangerous designer drug market was unleashed to circumvent the illegal status of drugs with a longer history and known biological profiles. Yet, designer drugs have been synthesized and marketed for decades, with or without controlled substance laws. Wherever there is a niche market, someone, somewhere will try to permeate it for profit. Public health and safety drive the views expressed below. The hazards of these drugs and the rationale for regulating and controlling access to them are based on a number of considerations:

(1) Emergency room mentions of designer drugs (and deaths), from Poison Control Centers, and from single case reports from physicians has escalated in recent years. These occurrences represent a significant public health and safety issue that requires regulatory intervention (Table 1).

(2) *The acute biological and behavioral effects and long term consequences are unknown: erring on the side of caution is sound public health policy.* Detailed biological effects and targets of many drugs have not been identified, nor do we know how they will react in the presence of other drugs in the body, or what potentially toxic contaminants are in the marketed mixtures. Currently, treatment of overdose crises or addiction is based on guesswork, or extrapolation by analogy to drugs with similar psychoactive effects. For the majority of these drugs, approved pharmacological antidotes do not exist and their projected biological targets can be far off the mark. For example, the sites of action of the unusual chemical SalvinorinA, a powerful hallucinogen produced by the plant *Salvia Divinorum,* baffled the scientific community. It bore no chemical resemblance to any of the known hallucinogens that target principally serotonin receptors (subtype $5-HT_{2A}$) in the brain, and was missing the element nitrogen, thought to be essential for hallucinogenic effects. A screening procedure finally identified a most unlikely primary target - the kappa opioid receptor. The kappa opioid signaling system normally can reduce pain, but can also produce unpleasant sensations or dysphoria (9). The chemical structure of SalvinorinA was so remote from conventional kappa drugs that this discovery sent shockwaves through the scientific community (Figure 1). How can a non-nitrogenous hallucinogen, that bears little resemblance to any known hallucinogen and has no biological effect on the targets of the majority of hallucinogens, serotonin receptor subtypes, be attracted by opioid receptors in the brain?

This is a dramatic example of how a newly discovered or a slightly altered drug can affect brain function unpredictably. Many of these drugs have not been extensively tested in controlled laboratory conditions; the responses they elicit in humans are gleaned largely from single case reports, from anecdotes, surveys, emergency department mentions, without the advantages of controlled clinical trials. How do they act? What are their

biological targets? What are the effects if a dose is increased by a factor of 3- or 10- or 100-fold? What if three or ten compounds are sold in the same mixture? Are their effects additive or synergistic or antagonistic? How long do they persist in the body? Do they interfere with sleep, cognition, memory, coordination, spatial, time, sensory perception? Do they produce hallucinations or psychosis? Are these drugs acutely toxic to brain cells or to other organs? Are they addictive? Are there long term adverse effects after repeated use? Are unwanted side effects irreversible? Do they interfere with cardiovascular, lung, kidney, endocrine, liver, immune or reproductive functions? Can they synergistically interact with other drugs (e.g. alcohol or medications) to create a health crisis? Do they interfere with absorption or metabolism of foods, medications or other safe, ingested materials? What would transpire if governments decided that some designer drugs have relatively low potential for harm and permit sale by regulated manufacturing processes? Would regulatory oversight of chemical synthesis absolve governments from public protection?

Another problem is the terminology "relatively safe". What criteria are to be applied to designate a psychoactive designer drug "harmful" or "safe"? Is harmful to be defined as: an acute illness? addictive potential? overdose crisis or death? impaired or loss of cognitive function? cardiovascular effects? hallucinations or delusions? loss of interest in responsibilities, school, work, parenting, other activities? Is harmful only to be scrutinized during an acute phase?

Time, or rather, an extended period of time is needed before scientific evidence and public perception/use patterns are in synchrony. One example of lag time between initiation of use and evidence for unacceptably high consequences is observed with early initiation of drugs. Early adolescent drug use is associated with a much higher prevalence of addiction, cognitive impairment, and other adverse consequences in adulthood (11, 13, 14). This pattern is consistent for early adolescent use of marijuana, alcohol, cocaine, amphetamines, nicotine, heroin, inhalants, and benzodiazepines. As designer drugs are analogs of this drug array, conceivably early initiation of

the majority of designer drugs will confer the same high risks for youth. Yet, prospective studies will require years or decades before an association is discerned.

Another example is the lag time between the rise of smoking as a socially acceptable behavior, and the decades of research that established smoking as a health hazard. Smoking tobacco had been practiced sporadically for at least 1,000 years in the Americas, but it was only after mass production of cigarettes - to over 300 billion cigarettes each year in the US – that use rates rose rapidly from the turn of the century to peak just past the mid-20th century. Recall that during this period of "immature evidence", the classic movie "Casablanca" was filmed in a fog of cigarette smoke. By the mid-20th century, the scientific evidence that smoking was the leading cause of lung cancer and a major cause of cardiovascular disease was overwhelming. The lag time between early acceptance of smoking as a harmless, or even a beneficial, glamorous social norm, and indisputable evidence for health problems was 50 years. When the Surgeon General of the United States publicized this major health risk in a detailed scientific report (1964), he catalyzed a striking change in national awareness and behavior (10). But during the 60 years that had lapsed, thousands of premature deaths and illnesses beset individuals and their families.

Marijuana consumption is another example of a divergence between public perception and scientific evidence. Marijuana has a much longer recorded history than tobacco. Yet, evidence for its adverse consequences, on cognition, addiction, psychiatric status, fertility, pulmonary, cardiovascular system, life-span, has taken decades to accumulate. Even so, the scientific data only rarely penetrates the mainstream media and public awareness. Only recently (August 2012) did marijuana receive significant negative press and public attention, with the publication of a report describing its IQ lowering effects in young initiators (11). Yet marijuana use continues to climb and states continue to approve marijuana as "medicine", to decriminalize it, by ballot initiatives or legislative acts.

(3) *Quality control does not exist. The public should be informed of criteria for "quality control" and why designer drugs do not achieve these criteria.* As research chemicals are prepared in clandestine laboratories, there is no regulatory oversight on quality control. In contrast, the list of regulations that govern approval and oversight of production of medications by the FDA is daunting and lengthy. Requirements include evidence that the synthesis is reproducible and each batch is identical, the dose range is known and safe, the shelf life is known and a safe date of expiration is known, the purity is "pharmaceutical grade" as even a 1% or less toxic impurity can have devastating effects, that each batch be tested for microorganisms, fillers are non-toxic and as pristine chemically as the drug itself, and the drugs are tracked by a chain of custody. Designer drugs do not fulfill any of these criteria and there is no assurance that these compounds correspond to the ones "marketed" or come close to achieving the standard of purity legally required for pharmaceuticals. Even if the company that markets the "research chemical" advertises purity levels or offers documentation of purity, there is no guarantee that these documents accurately reflect the quality of the purchased material, without legalization and regulatory oversight. Obviously, designer drugs are not subject to the same pre-clinical and clinical trials required for approval as a pharmaceutical agent. With years of chemical, biological, metabolic, behavioral, toxicological testing in animals and years more of randomized, controlled, multi-centered clinical trials in thousands of subjects, and hundreds of millions of dollars expended for this costly research, the drugs that have passed through this "firewalk" and finally are approved for human use by the FDA, have a measure of safety and efficacy that no designer drug can claim. With or without regulatory oversight, individuals' adverse responses to the drugs generally emerges only during crises, with critical information gleaned from emergency rooms, physicians, and surveys rather than from controlled clinical trials.

3. Current illegal drugs and designer drugs

Some claim that current restricted illegal drugs are relatively "safe" compared with designer drugs and should be legally available. If viewed in the context of the prevalence of addiction to marijuana, psychostimulants, opioids, the incidence of adverse medical, educational, occupational, safety and social consequences, this view is unsupportable. From the perspective of prevalence of use, of adverse consequences and the potential for effective preventive measures, a choice between two preventable risks to human health and safety is not sound public health policy (12-14).

(1) During the 1960's, a time period when choices between current Schedule I (e.g. marijuana, LSD) and "designer drugs" did not exist (the Controlled Substance Act passed in 1973), a wide range of designer drugs, including hallucinogens flooded the market and were absorbed by the culture. The incentives then were the same as they are today, to offer users novel sensations and experiences, expand markets to new users, undermine the profits of "conventional producers", profit from chemical, and not agricultural production, and evade legal sanctions.

(2) The drugs that currently are the leading cause of morbidity (illness and overdose) and mortality (overdose deaths) in the US are not Schedule I drugs, the most restrictive category, but legal prescription opioids. In this case, the legal status of opioids has not curtailed overdose deaths, but the designation as a scheduled prescription opioid most likely reduces its non-medical use.

(3) The potencies of conventional drugs (e.g. marijuana) have increased considerably over the past decade; increasing potency has paralleled increasing emergency room mentions and increased addiction prevalence. There are no guarantees that the production, strength and the current "safety" profile of Schedule I drugs will remain stable or "safer" than designer drugs.

(4) Drug control clearly has a significant impact on reducing overall use, on public perception of drugs and on their risks. There is evidence that the legal status of designer drugs drives use among those attracted to experimenting with designer drugs and discourages users seeking only "legal drugs" (15,16).

(5) Intoxicating, psychoactive drugs that are marketed legally, (e.g. inhalants, alcohol, nicotine, or prescription opioids), can also result in massive public health problems and premature deaths (17).

(6) Some politicians, drug use advocates and scientists claim that emergency and permanent scheduling of drugs are burdened with an unintended consequence: interference with research on the potential benefits of these drugs. Yet a search of the National institutes of Health database and the medicinal chemistry literature reveals robust research with Schedule I drugs, their derivatives, and with novel, unscheduled drugs. A fraction of these will evolve into medications, while others may be diverted into the squalor of street drugs. At times, some unintended consequences materialize from scientific curiosity and motivation to develop effective medications. The majority of designer drug structures and routes of synthesis were gleaned from manuscripts published in high quality journals and from patents. Medicinal chemists and pharmacologists seeking biological clarity or improved therapeutics agonize over the appropriation of their creative science by clandestine chemists, which use the inventions of those motivated to improve health and seek understanding, to market hazardous chemicals that compromise health.

C. The Designer Drugs

Current designer drugs can be classified by their chemical structure, by their psychoactive properties, by their known biological targets, or by their source (plant, synthetic, or combined) (Figure 2).

1. Stimulants: The "Bath Salt" Cathinones

The drugs most found in "bath salts" are substituted cathinones (synthetic derivatives of the stimulant chemical in Khat). "Bath salts" are disguised as plant foods, insect repellent, bath salts, stain removers, and sold under brand names such as Bliss, Blue Silk, Cloud Nine, Drone, Energy-1, Ivory Wave, Lunar Wave, Meow Meow, Ocean Burst, Pure Ivory, Purple Wave, Red Dove, Snow Leopard, Stardust, Vanilla Sky, White Dove, White Knight, and White Lightning. The products are sold as powders in small plastic or foil packages of 200 and 500 milligrams. The chemical compositions vary widely, as do purity and safety. Prior to current and ongoing DEA classification of these drugs in Schedule 1, distributors continue to package and market them deceptively.

The structure of phenethylamine, a trace amine found in the brain, is the backbone for most of the stimulant-type designer drugs (Figure 2). These compounds are easy to prepare and can be chemically fashioned in a myriad of ways to produce stimulants (amphetamine), stimulant-like hallucinogens or "entactogens". Variants currently in the research domain or in the illicit drug market are a small fraction of the possible drugs that can be conceived of and synthesized. Cocaine- and amphetamine-like psychostimulant drugs of abuse, mephedrone, methylone, and pyrovalerone analogs, including MDPV, and naphyrone are some of the chemicals packaged as "bath salts". These drugs are typically self-administered by injection, smoking, insufflating, gingival delivery, via intramuscular or other routes (18). The products have been widely available in the United Kingdom for several years, but emerged in the United States in the past three years. Nationwide, typical male and female abusers of these substances range from teenagers to those in their 40s. Users often have an extensive history of drug abuse. Some abusers describe the effects as similar to methamphetamine, ecstasy, and cocaine, and have referred to the substances as "complete crank" while others use the term "fake cocaine or "fake MDMA" (16, 18, 20, 21, 26).

These putative inhibitors of transport of brain monoamines all produce psychostimulation, possible "empathic responses" and cardiovascular effects, consistent with alterations in dopamine, serotonin and norepinephrine biology. They can also produce extreme agitation and life-threatening cardiovascular crises, which accounts for the steep rise in emergency department mentions. A paucity of information exists on the biological, physiological and toxicological effects of these drugs, especially their long term effects after heavy and prolonged use.

Collectively, the subjective effects of synthetic cathinones have been reviewed (18, 19). The spectrum of psychoactive effects include aggression, dizziness, memory loss, seizures, blurred vision, anxiety, hallucinations, depression, dysphoria, euphoria, fatigue, increased energy and decreased concentration, panic and paranoia. Other reported effects are palpitations, shortness of breathe, chest pain, dry mouth, abdominal pain, anorexia, vomiting, erectile dysfunction, discoloration of the skin, and muscular tension. Clinical symptoms reported by healthcare providers involve the majority of organ systems: psychiatric, neurological, gastrointestinal cardiac, pulmonary, renal, eyes, ear, nose, and throat. There is no consistent information on the addictive potential of these drugs, but based on the structures, their resemblance to amphetamines and cathinones, and modes of action, it is likely that most will have addictive potential. In several surveys of mephedrone users, 50% considered it to be addictive, nearly half reported continuous use for more than 48 hours, and more than 30% reported fulfilling three or more criteria for abuse/addiction, according to DSM-IV (20). A different survey (n=1,006) found that 17.5% of users reported symptoms of addiction, with the highest frequency of daily use falling in the 11-15 year old age range (21).

1a. Mephedrone

Mephedrone or 4-methyl-*N*-methylcathinone is a synthetic compound first synthesized in 1929 and rediscovered in 2003. Its root structure overlaps with cathinone from Khat plant, and has structural features in common with

amphetamine and phenethylamine (PEA), a chemical signal produced by the brain that activates a trace amine receptor1 (22). Mephedrone reportedly became available via internet sales in 2007, and has become prevalent in many European countries, in Asia, Australia, New Zealand, Israel, the US and Canada. Unconfirmed reports of deaths, a high number of emergency room mentions and addictive potential associated with its use has resulted in its classification as an illegal substance by United Kingdom (April 16, 2010) and the EU in 2010 (23). On the one hand, distribution and use of mephedrone continues and users may be replacing MDMA with mephedrone (24-27). On the other hand, an analysis of presentations to the emergency department of patients with acute toxicity related to the use of mephedrone demonstrated that there was a peak in presentations prior to and a significant fall in presentations following legal restrictions on mephedrone. This suggests that mephedrone control may have been effective in reducing the acute medical crises associated with the drug (15).

Psychoactive effects of mephedrone. Possible leads on mephedrone's biological activity, and toxicology, are derived from human self-reports, emergency department mentions and preclinical research. The majority of reports claim that mephedrone is a psychostimulant, with effects similar to those of cocaine, amphetamines and MDMA (ecstasy), after ingestion, i.v. injection, rectal administration, or insufflation as a powder, pill or capsule. Insufflation is the most common routes of administration (25-29). Although 56% of users reported adverse consequences in one survey (19, 21), respondents also reported intense stimulation, alertness, euphoria (consistent with cocaine or amphetamine effects), empathy and increased intensity of sensory experiences (consistent with MDMA effects), mild sexual arousal and perceptual distortion at high doses (28). In an acute study that compared 20 mephedrone users (a) during intoxication, (b) drug free and with (c) non-using controls, mephedrone users had impaired prose recall, higher scores in schizotypy and depression, primed a marked 'wanting' for the drug, induced stimulant-like effects, impaired working memory and enhanced psychomotor speed, in an average mephedrone session lasting nearly 8 hours (30).

Emerging as a drug of choice for some, mephedrone, has addictive potential. Users reported binge use, an inability to abstain, and use until supplies are depleted or symptom severity requires medical attention. Recent surveys found that 15-20% of users reported using weekly or more frequently in England (20, 21). Most disconcerting is the finding that 13-15 year olds had the highest percentage of daily use. Intranasal use is associated with higher self-reports of mephedrone as an addictive drug. More than half reported that the duration of the "high" and the quality of the "high" was better with mephedrone than cocaine. These behavioral patterns converge on mephedrone as an addictive drug, with a profile similar to responses engendered by high doses of cocaine, amphetamine or MDMA (29). In a survey of high schools and colleges, 17.6% of users reported addiction or dependence on mephedrone (21). Recent reviews of mephedrone documented in detail the known prevalence of use in the UK, and its acute and toxic effects of the drug (3, 19). Collectively, the reports provide compelling reasons to regulate and then clarify the biological and long term effects of mephedrone and related drugs.

Adverse consequences of mephedrone: psychoactive, cardiovascular and addictive properties. The adverse effects of mephedrone are derived from analyses of emergency department mentions, single case reports, and self-reports from interviews. At least 56% of users report adverse consequences (19-21, 31-36). These range from inability to concentrate, inability to focus visually, memory problems, nasal irritation, nose bleeds, loss of appetite, nausea, vomiting, tremors, headaches, hyponatremia with encephalopathy, psychiatric symptoms, crushing chest pain, urination difficulties, changes in body temperature (hot flushes and sweating), discoloration of extremities, tremors, convulsions, insomnia, nightmares, hallucinations, delusions, and immunological toxicity. In several reports relating to mephedrone toxicity (34-36), subjects were identified with mephedrone complications including psychoactive and cardiovascular toxicity. Of mephedrone patients, 51% were admitted, reflecting symptom severity. Adverse symptoms include agitation, aggression, anxiety, parasthesia, palpations, shortness of breath, confusion, collapse, paranoia, hallucinations, aggression, peripheral vasoconstriction, pain, and seizures. Heart rate, sinus tachycardia, and blood pressure were elevated, in some cases to extreme levels,

while temperature was low to normal. Most of these symptoms were associated directly with mephedrone. In a series of analytically acute mephedrone toxicity presentations to an ED, the clinical features were consistent with an acute sympathomimetic toxicity including hypertension, tachycardia and agitation (3, 15, 37-39). These findings are similar to the pattern of toxicity seen with other sympathomimetic drugs such as MDMA, amphetamine or cocaine. At least 60 cases of mephedrone-suspected deaths have been reported in the UK. In one confirmed case of mephedrone fatality, stomach levels were 115 mg and blood levels reached 5 mg/L, equivalent to 28 µM (40). These blood levels are rarely seen with any legal or illegal psychoactive drug!

Possible mechanisms of action. Similar to related cathinones and amphetamine-type drugs, mephedrone affects signaling of dopamine, serotonin and norepinephrine in the brain. These three chemical messengers (also known as biogenic amines, monoamines, or neurotransmitters) transmit signals between nerve cells in the brain and in other organs. They are critical for a wide range of functions in the brain and peripheral tissues, including reward, mood, learning and memory, alertness, motor activity, sleep, sexual behavior, hormone release, heart rate, pain perception, blood pressure, platelet aggregation, and others. Mephedrone and its related analogs affect the brain levels of these transmitters by interfering with mechanisms that are critical for regulating their concentrations. These designer drugs target transporters – complex proteins located on or in nerve cells that control, with exquisite precision and in millisecond time frames, the amount of transmitter available for signaling. Mephedrone and similar cathinones bind to these transporters, either blocking them or "tricking' the transporter to carry them into the nerve cells (41-49). The net effect is to release vast quantities of monoamines; the inundation conceivably produces the euphoria that promotes "liking" and "wanting" the drug.

In preclinical research, mephedrone lowered body temperature and heart rate, increased locomotor activity and intracranial self-stimulation in rodents, elicited conditioned place preference (a measure of rewarding properties) and produced psychomotor stimulant effects similar to methamphetamine in nonhuman primates (41-49).

Mephedrone blocked dopamine and serotonin transporters, elevating monoamines to levels observed with MDMA and other amphetamines.

1b. Methylone

Biological, psychoactive effects of methylone. Methylone has minor structural changes similar to scheduled drugs, e.g. cathinone (Figure 2). It acts on monoamine transporters (dopamine, norepinephrine, serotonin), blocking the transport of these critical transmitters in the brain, serving as a substrate for the transporters, and promoting the serotonin. These biological effects are similar to amphetamine-like psychostimulant drugs and Ecstasy (42-44, 49) and produces locomotor activity, in accord with its effects on dopamine (44).

Adverse effects of methylone. Increasing case reports exist on the morbidity and mortality associated with methylone. One example described "a case of a healthy 24-year-old who ingested a capsule containing methylone and butylone sold as "Ecstasy" at a concert. The patient presented to the emergency department comatose, with high fever, rapid heart rate, high blood pressure, and seizure-like activity. Despite maximal medical care, she suffered multi-system organ failure and died. Laboratory analysis identified only methylone and butylone in a capsule found in her belongings and in her urine (50)." More reports of medical crises and fatalities attributable to methylone are beginning to appear in the biomedical literature (50-53).

1c. 3,4-Methylenedioxypyrovalerone (MDPV)

Pyrovalerone was developed in the 1960's as a treatment for chronic fatigue and obesity, but it was removed as a therapeutic drug because of its abuse liability. A drug patent reported its potency as higher than methylphenidate. MDPV is a psychostimulant analog of cathinone, but derived from pyrovalerone. It became a

drug of abuse in 2008, marketed in the US as "bath salts" and as an intoxicant with effects similar to cocaine, amphetamine, or MDMA. A growing body of scientific, emergency room mentions and other sources of information on MDPV's acute psychoactive effects, toxicity and pharmacology (e.g. the DEA, the Psychonaut Web Mapping Research Project MDPV report) created the necessary support for the UK and DEA decision for emergency scheduling (1,2,7,8,18,23,54-61). Yet, the internet persists as a major source for purchase. MDPV reportedly has similar biological effects as mephedrone, cocaine, methamphetamine, and methylphenidate, producing stimulation, increased energy, mild empathogenic effects. Taken by insufflation, orally, intravenous, smoking, or other routes, the drug can produce a profound health crises of 6-8 hour duration. Its acute psychoactive effects can range from severe paranoia, hallucinations, psychosis, suicidal ideation, self-mutilation, aggressive, violent of self-destructive behavior. It also affects other organ systems, reportedly producing rapid heart rate (tachycardia) hypertension (high blood pressure), heart arrhythmias, high body temperature, sweating, insomnia, stomach cramps, grinding teeth, increased body temperature, chills, sweating, headache, bloodshot eyes, kidney pain, ringing in ears or dizziness, breathing difficulty, agitation and panic attacks. In an acute emergency, seizures, stroke, brain swelling (cerebral edema), heart attacks, collapse of the cardiovascular system, and death can occur (54-61). High frequent doses reportedly cause intense, prolonged panic attacks in intolerant users, psychosis from sleep withdrawal, craving and addiction. In preclinical studies. MDPV maintained self-administration and lowered the threshold for intracranial self-stimulation, properties characteristic of other highly addictive drugs in humans, such as methamphetamine (62).

1d. Naphyrone or naphthylpyrovalerone

Naphyrone was produced in a medications development program (63) in an effort to discover new treatments for psychostimulant addiction. Lipophilic analogs of pyrovalerone were designed to reduce its rapid entry into brain and associated abuse liability. It was then diverted and sold in the illicit drug market as "pond cleaner" as a psychostimulant substitute for mephedrone (NRG-1, infrequently containing naphyrone) or as "glass or jewelry

cleaning agent" (64). In July 2010, it was placed under control in the UK as a public health hazard (1). Naphyrone inhibits dopamine, norepinephrine and serotonin transporters in the nM range in vitro (43, 63), but there is scant other biological or behavioral data in peer-reviewed journals. A single case study reported that a 31-year-old man ingested a dose of naphyrone (100 mg), which produced acute sympathomimetic toxicity with restlessness, insomnia, anxiety, and hallucinations lasting for two days. Naphyrone was detected in the patient's plasma by gas chromatography with mass spectrometry after drug intake (65). In another case study, a user bought what he reportedly thought was the legal compound naphyrone (NRG-1) but in fact was MDPV and butylone. After ingesting a massive 1 gram dose, he developed palpitations, sweating and insomnia (66).

Summary. Not all cathinones are the same, with each conferring a different set of health risks. Nonetheless, use of cathinone analogs is increasing rapidly, especially among youth and in the face of mounting evidence that they engender unacceptable risks and adverse consequences: (a) emergency department mentions, (b) persistence of effects after 24 hours, (c) addictive potential, (d) psychiatric and cardiovascular effects, and (e) deaths. We urgently need a national and international response that imposes further legal restrictions, expands public education efforts, and education of health care professionals.

2. Cannabinoid designer drugs: "Spice", "K2"

The annual Monitoring the Future (http://www.monitoringthefuture.org/) survey of high school students, for the first time in 2011, surveyed the use of "Spice or "K2", but only in 12th graders. *An astonishing 11.4% had used some form of synthetic cannabinoids in the past year!*

2a. Cannabinoid biology

There are three types of cannabinoids: (1) Phytocannabinoids - are cannabinoids produced by plants. The marijuana plant produces over 70 phytocannabinoids. Δ^9-TetraHydroCannabinol or THC is found at much higher concentrations than any other cannabinoid in the common *Cannabis Sativa* plant, one of several plants that produce cannabinoids. (2) Endocannabinoids - are produced by the brain and other organs. The body produces seven or more endocannabinoids, two of which are widely distributed and function in cannabinoid signaling: anandamide (2-arachidonoylethanolamide) and 2-AG (2-arachidonoylglycerol), which resemble, but are not identical to cannabinoids of plant origin. (3) Synthetic cannabinoids - were developed over the last 30 years as research tools to investigate cannabinoid systems in the brain and other organs and to explore the feasibility of developing cannabinoid medications (Figure 3).

What are the functions of endocannabinoids? Cannabinoid communication or signaling system has three major components: (1) a chemical message or neurotransmitter (e.g. endocannabinoid), (2) a receptor that interprets the message, and (3) an enzyme that degrades the message. The system has ancient evolutionary origins, with components discovered in a range of vertebrates, and possibly some invertebrates. Endocannabinoids activate two types of proteins, the CB1 and CB2 cannabinoid receptors. These receptors have a myriad of functions in the body that influence functions of the brain, heart, testes, uterus, prostate gland, vascular tissue, immune cells, adrenal gland, and the intestinal tract. The CB1 receptor is the target of THC, the most active constituent of the marijuana plant, whereas the CB2 receptor, a weak target of THC, functions primarily in peripheral tissues, and specifically in the immune system. With the discovery of these receptors and the host of endocannabinoid functions throughout the body, medicinal chemists produced thousands of synthetic cannabinoids, seeking to discover cannabinoids that possess therapeutic, but not psychoactive properties (67, 68), or to probe the cannabinoid signaling system to clarify their role and how marijuana produces profound psychoactive effects. With this large array of synthetic cannabinoids, and the precedent established by designer opioids, stimulants and hallucinogens, it was predictable that some cannabinoids would be extracted from legitimate research/development documents and diverted to the clandestine marketplace.

2b. Synthetic "designer" cannabinoids

Trafficking of synthetic cannabinoids was first reported in the United States in a December 2008 encounter, in which a shipment of "Spice" was seized and analyzed in Dayton, Ohio. Sold as "legal" alternatives to marijuana, synthetic cannabinoids originally were confined to a few compounds, (e.g. JWH-018 or 1-penthyl-3-(1-napthoyl)indole), but others rapidly followed. JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol have been found alone or laced on products that are marketed as herbal incense. The popularity and abuse of these substances and associated products has spread rapidly since 2008. Prior to being temporarily placed in Schedule I on March 1, 2011, "K2" and "Spice", they were marketed under the guise of "herbal smoking mixtures", "incense", "herbal blends", "air freshener" and designated "not for human consumption". Promoted as legal alternatives to marijuana, they became widely available over the Internet, and sold in gas stations, convenience stores, tobacco and head shops to all populations (69, 70).

Some synthetic cannabinoids are relatively old compounds dating to the 1960's and 1970's, while others are of more recent vintage. Warnings regarding the dangers of synthetic cannabinoids and associated products have been issued by numerous state public health departments and poison centers and private organizations. Detailed product analyses show wide variations in the amount and type of synthetic cannabinoid laced on the plant material.

Biology. All designer cannabinoids mimic the psychoactive effects of marijuana, with some considerably more potent than marijuana at the cannabinoid CB1 receptor. Their metabolites may differ biologically from marijuana (7, 70). Users perceive synthetic cannabinoids as another form of marijuana, but in the absence of detailed research, there exists serious safety concerns, because the adverse side effects are pronounced with synthetic

cannabinoids: agitation, hallucinations, psychoses, seizures, hypertension, panic attacks. For example, some of the metabolites of these compounds do not activate CB1 signaling, but prevent it, causing the opposite effect of endocannabinoids or marijuana. Some are active at the CB2 receptor which could significantly affect the immune system. In preclinical studies, drug discrimination procedures test whether a drug produces the same physical or subjective perceptions similar to those produced by a known drug of abuse. Drug discrimination studies in monkeys suggest that controlled synthetic cannabinoids (JWH-018, JWH-073) have similar subjective effects as THC (71). In the test tube and animal studies, the pharmacological effects of JWH-018, JWH-200, JWH-073, CP- 47,497 and cannabicyclohexanol are similar to those of THC. The CB1 receptors are thought to be responsible for the euphoric and psychoactive effects of THC and related cannabinoids (72). As with THC, JWH-018, JWH- 200, JWH-073, CP-47,497 and cannabicyclohexanol have agonist properties at the CB1 receptor.

Acute effects. Numerous anecdotal self-reports, case reports and series indicate that these substances are abused by humans for their hallucinogenic effects. The abuse of synthetic cannabinoids has been associated with both acute and long-term public health and safety concerns. As of December 31, 2011, the American Association of Poison Centers has reported receiving 9,992 calls corresponding to products purportedly laced with synthetic cannabinoids. The calls represented exposed individuals from all 50 states and the District of Columbia, Puerto Rico, U.S. Territories, foreign countries, and a overseas/US military/ diplomatic. Several of these exposures were confirmed to involve JWH- 018, and JWH-073. With evidence of abuse and adverse health effects on a national scale, state public health and poison centers have issued warnings of herbal incense products containing these synthetic cannabinoids (7, 69, 70).

Systematic reviews of this class of agents reveal both acute and long term effects (69, 70). Acutely, a few case studies report that Spice produces pleasant and euphoric sensations to anxiety, psychomotor agitation, cognitive impairment, palpitations and in a single case, generalized convulsions (73). Although symptoms vary with

individuals, typical effects can include marijuana-type symptoms, relaxation and sedation, euphoria, while others report agitation, illness, eye soreness, and mpaired short-term memory and concentration.

Case reports describe presentations to emergency departments of individuals exposed to synthetic cannabinoids with severe symptoms that include anxiety and panic attacks, tremors, generalized convulsions, psychosis, heart palpitations and elevated pulse, severe gastrointestinal distress, tremors, blurred peripheral vision, nausea, and persistent vomiting with retching (70). Such abuse also includes instances of persons suspected of driving under the influence of these synthetic cannabinoids, including one incident where an automobile was driven through a residence. In that case the driver claimed to have no memory of the event while a toxicology analysis confirmed that the driver had smoked a product containing JWH-018, but not any other drugs (7). Other symptoms of severe acute toxicity that can endure for as long as 10 hours may include delirium, impaired coordination, sleeplessness, seizures, palpitation, agitation, headache, paranoid hallucinations, confusion, mood disorders, and psychotic symptoms that can persist long after the last dose. Serious effects of these synthetic cannabinoids can also be manifest as tachycardia (rapid heart rate), loss of consciousness, diarrhea, nausea, and vomiting. There are also three reports of myocardial infarction (heart attack) in healthy adolescents (74) but this was not confirmed by detailed chemical analysis of the ingested material. Severe toxicity, with seizures, vomiting, agitation after smoking Spice has been documented (75).

Long-term effects. The pharmacological profile of JWH-018, JWH-200, JWH-073, CP- 47,497 and cannabicyclohexanol strongly suggests that they possess physiological and psychological dependence liability similar to that of the Schedule I controlled substances marijuana and THC. Physical and psychological withdrawal symptoms are manifestations of biological adaptation in the body. Some reported withdrawal symptoms included elevated blood pressure, restlessness, drug craving, nightmares, sweating, nausea, tremor and headache, palpitation, insomnia, headache, diarrhea, vomiting (69, 70, 76). Because these substances act through the same molecular target as THC, the main active ingredient of marijuana, it can be reasonably expected that

their physical dependence liability will be similar. Long-term, regular use of marijuana can lead to physical dependence and withdrawal following discontinuation as well as psychic addiction or dependence.

Adding to these concerns are reports of new-onset of psychosis in otherwise healthy males reportedly smoking synthetic cannabinoids frequently and reports of the drugs exacerbating psychotic episodes (77-79).

2c. *Legal status of synthetic cannabinoids*

On March 1, 2011, several of these synthetic cannabinoids were temporarily placed into Schedule I by the DEA, imposing criminal sanctions and regulation of their manufacture, distribution, possession, importation, and exportation and this was extended into 2012 (7). As of early 2012, at least 48 states have banned one or more of this class of drugs. They are legally available for research purposes. The evidence underpinning this decision was based on health and safety considerations. If taken in sufficient amounts, the toxic effects were similar to those induced by high doses of marijuana (anxiety, tachycardia and hallucinations) but also include seizures, tachyarrhythmias, extreme anxiety. The precipitation of psychotic episodes has also been reported following abuse of these substances or products containing these substances.

There is no currently accepted medical use for any of the five described synthetic cannabinoids, and, outside of a limited research setting, no medical practitioner is currently licensed by law to administer them. HHS states that JWH-018, JWH-073, JWH-200, CP-47,497 and cannabicyclohexanol are cannabinoids with a potential for abuse similar to the Schedule I substances marijuana and THC. These synthetic cannabinoids appear to be marketed solely for abuse of their marijuana-like activity and because, prior to the March 1, 2011, they were not controlled under the CSA. As such, commerce involving these synthetic cannabinoids can only be for the purposes of abuse and escaping the regulatory and criminal penalties of the CSA that pertain to marijuana.

The increased abuse of these synthetic cannabinoids in the United States is supported by an increasing number of encounters by law enforcement. Over the past year in the United States there has been a significant increase in availability, trafficking and abuse of these substances as evident from the increasing number of encounters reported by forensic laboratories. Product manufacturing and synthesis laboratories have been discovered, and laboratories have been found manufacturing products by lacing plant material with synthetic cannabinoids. Two suicides, one also involving a murder, have been linked to the abuse of synthetic cannabinoids (law enforcement communication to DEA, 7).

Summary. "Spice" and "K2", especially as they are widely used by high school and college students, are emerging public health challenges (80). Their rapid rise in popularity, ready access from multiple sources, production of acute psychological distress, toxicity and potentially long term harmful effects, ability to evade standard drug tests, require an integrated national response. Healthcare professionals, law enforcement, testing capabilities, a massive public education campaign and strategies for deterrence in healthcare systems are needed to respond to this emerging threat.

3. *Hallucinogens and other emerging designer drugs: A brief overview.*

A number of hallucinogens and other psychoactive drugs have evolved into street drugs: (1) phenethylamines (similar to mescaline), rigid analogs of phenethylamines and benzylphenethylamines (e.g. 2C-Bfly, Br-fly, Br-dragonfly); (2) SalvinorinA, *which the 2011 Monitoring the Future survey showed past year use rate of 5.9% among 12th graders!* (3) tryptamines; (4) the dissociative anesthetics methoxetamine, ketamine, and PCP. Phenethylamine derivative potencies (e.g. amphetamines, mescaline) have been increased by locking the structure more rigidly to produce compounds designated as "fly" (Figure 4). Some are extremely potent and one (Br-dragonfly) is associated with an overdose death (89).

DMAA (1,3-dimethylamylamine), a common ingredient in "party pills" and some weight loss and sports performance supplements was regulated in Europe. DMAA has been linked to a range of health concerns, including increased blood pressure, headaches, vomiting and severe cases of cerebral hemorrhage or stroke (81).

A systematic survey of these drugs is outside the scope of this manuscript. Readers can glean an appreciation of the magnitude of the problem, the challenge of law enforcement in tracking all the possible compounds that can be made, and their behavioral, psychological and biological effects in an excellent review (6), and in other sources (81-91).

D.   Policy Recommendations

In 1982, seven young heroin addicts in Santa Clara County, California, were diagnosed with severe and unremitting cases of Parkinsonism after a street purchase and injection of, what they presumed was synthetic heroin (the meperidine analog MPPP or 1-methyl-4-phenyl-4-propionoxy-piperidine). Their bodies were frozen, bent over and immobilized, as if they were elderly, late-stage Parkinson's disease patients. Three that had been followed survived from 3-16 years. The clandestine chemist that produced MPPP allegedly had ripped the pages that describe the synthesis of meperidine and MPPP out of a medicinal chemistry journal from a university library, as the journal was found with these pages missing. Allegedly, the incompetent chemist had changed the synthetic procedure to accelerate production (by heating the mixture to a higher temperature than in the original "recipe") and did not test the final product for purity. The product was contaminated with a chemical neurotoxin, MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine) which destroys the same dopamine nerve cells that degenerate in Parkinson's disease. Parkinson's disease is a neurodegenerative disease of mostly elderly people, characterized by tremor, rigidity, slow movements, and impaired balance. In collaboration with the National Institutes of Health, the neurologist Dr. J. William Langston tracked

down MPTP as the cause (92). In 2008, another drug, methylcathinone was implicated, but not yet proven, as a new source of drug-induced parkinsonism in central Europe (93).

These two, egregious examples of the hazards of street drugs can be expanded into a multitude of cases. In an era of modern chemistry, modern communications, and modern marketing, can we interrupt the progression of drug-related public health problems? With resolve and effective strategies, the guardians of public health can triumph in this seemingly perpetual race against the distributors, who devalue or are indifferent to the well-being of consumers. Resolve, effective, rapid responses and public awareness are critical.

1. **Designer drugs: an international problem requiring international cooperation.**

▪ Coordinate international monitoring activities involving health professionals, researchers and law enforcement to glean and identify emerging drugs, sources, consequences via the internet, using automated web-crawling systems that require minimal diversion of resources.

▪ Collate and categorize synthetic drug information on a website to share with relevant agencies, including prevention and treatment communities, state departments, law enforcement, and internet monitoring sites. Develop a uniform set of international guidelines on what criteria should trigger emergency regulations.

▪ Based on these guidelines, identify gaps in information needed for legal restrictions on specific drugs or categories.

▪ Coordinate international law enforcement policies on marketing and sales of designer drugs. Easy access to these chemicals sources should be restricted by international laws, agreements, and local enforcement.

- Routinely monitor websites for traffic to and from producers.

2. National response

- Implement a comprehensive internet site for real-time entry, by health care providers, school officials, emergency departments, poison control centers law enforcement, of emerging threats and medical crises; ensure quality by designating credentialed individuals for data entry; create national awareness of its existence.
- Implement nation-wide, state-wide and local surveys of designer drug trends in schools, workplace (e.g. National Survey on Drug Use and Health, Monitoring the Future).
- Implement nation-wide, state-wide and local surveillance of healthcare centers (primary care, clinics, hospitals), with uniform questionnaires, case records and samples for biometric monitoring.
- Implement a national, standardized testing facility of samples to decipher chemical identity and chemical signatures (e.g. Department of Defense model).

3. Prevention and deterrent programs

- Create a single web-site that collates ongoing information and translates it to the public.
- Create a mechanism for press releases and releases into internet sites including social media (e.g. Twitter, Facebook, others) to alert the public on emerging drugs and their hazards.
- Create a prevention team that prepares internet accessible presentations for parents, teachers, community groups, universities, and schools.

- Create a method for raising awareness of and distribution of this information, to penetrate schools and universities, parents, teachers, and student populations.

- Develop a rapid response team including expertise in chemistry, biology, emergency room medicine, law enforcement, and media to respond to surges of specific drugs in local microenvironments. Each specialist should provide alerts and bulletins to colleagues for widespread distribution and public education.

- Incorporate designer drugs into standard Screening, Brief Interventions, Referral to Treatment (SBIRT) questionnaires.

4. Law enforcement

- Coordinate international regulations.

- Develop guidelines for "cut-off" of the amount of information necessary for emergency scheduling.

- Strengthen and enforce precursor laws.

- Monitor international research laboratories and enforce laws, as applicable.

- Identify rogue laboratories, their locations, and disseminate the information to the public.

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Figure Legends

Figure 1. Comparison of the structure of a conventional kappa drug (butorphanol) and the active ingredient of Salvia divinorum (SalvinorinA). Both target the kappa opioid receptor in the brain with butorphanol an analgesic (pain-killer) and SalvinorinA a hallucinogen. SalvinorinA is the first known compound acting at the kappa opioid receptors that is not an alkaloid (no amine nitrogen in its structure). The amine nitrogen in butorphanol is shown with an arrow). Photo of the mint plant *Salvia divinorum* that produces SalvinorinA.

Figure 2. Phenethylamine, the core structure of many designer drugs, is a neuromodulator produced by the brain which activates the Trace amine Receptor 1 or TAAR1 (22). Designer drugs are similar to amphetamines (amphetamine, methamphetamine, 3,4-methylendioxymethamphetamine or MDMA) and to the phytochemical cathinone, the active constituent of the Khat plant. Even subtle modifications can yield profoundly different behavioral, neurochemical, and neurotoxicological effects. For example, methamphetamine and methcathinone induce persistent dopaminergic and serotonergic abnormalities, while MDMA and mephedrone only induce serotonergic abnormalities.

Figure 3. Structures of phyto-, endo- and designer cannabinoids. Note how different the brain's own endocannabinoid anandamide, differs from the plant product (THC) and the synthetic cannabinoids (JWH-018). Even subtle modifications can yield profoundly different and unpredictable behavioral, neurochemical, and neurotoxicological effects.

Figure 4. Emerging designer hallucinogenic drugs: the rigid structures of the "flies".

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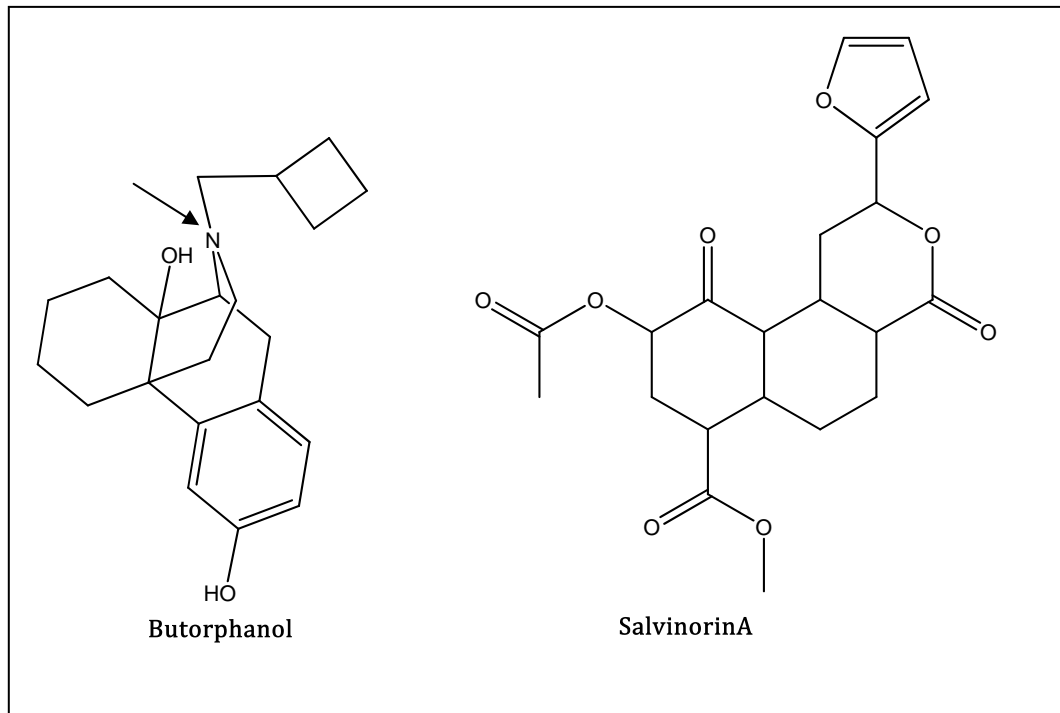

Butorphanol   SalvinorinA

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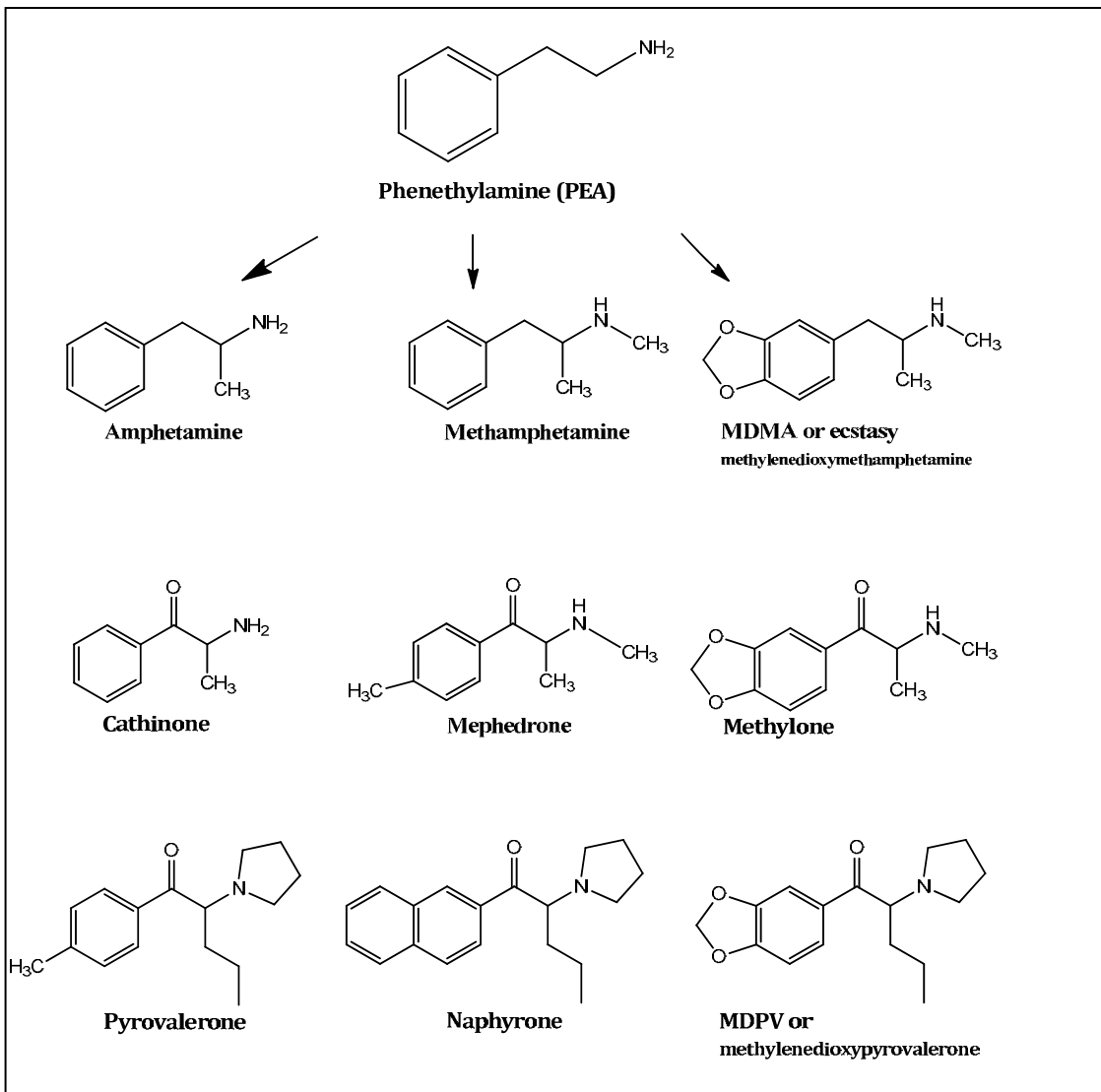
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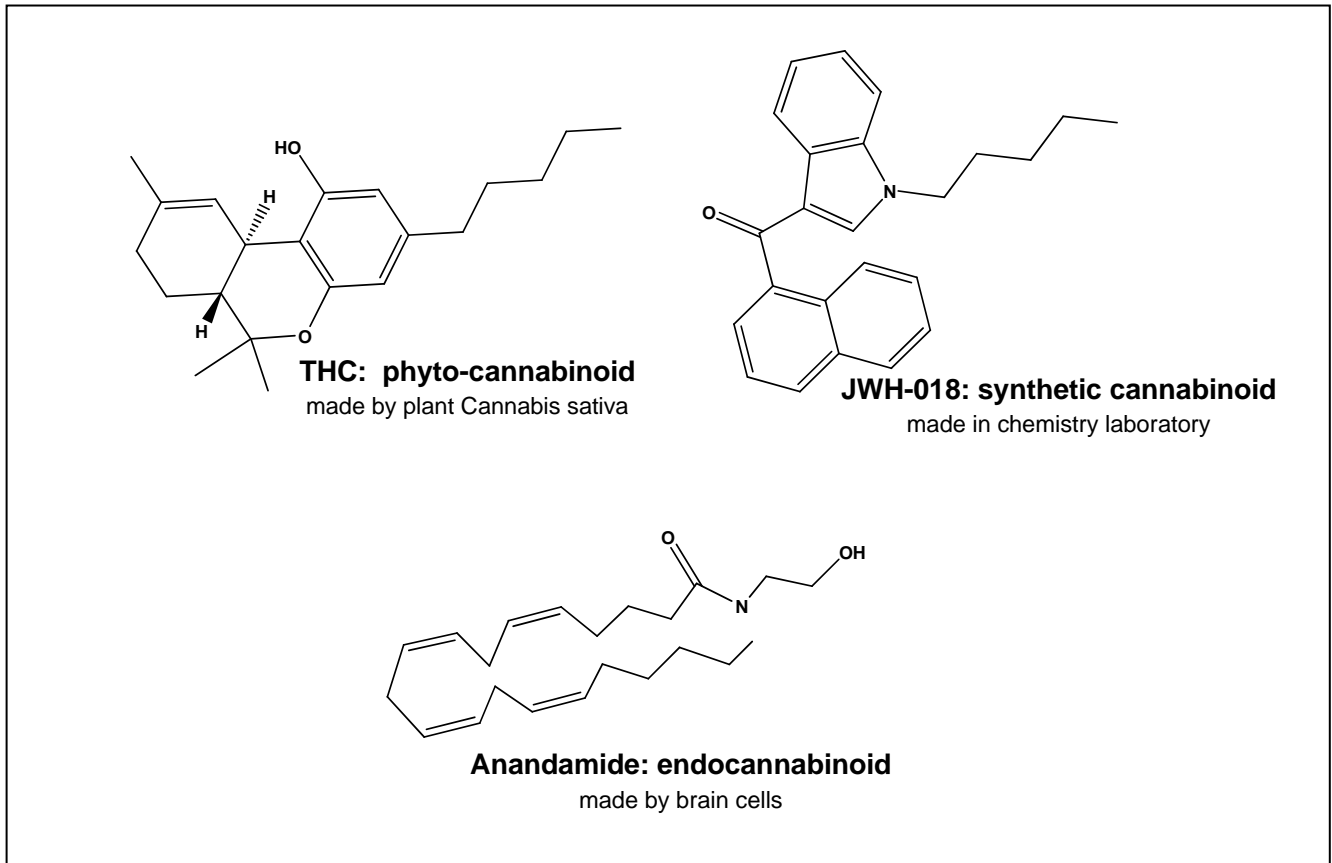

THC: phyto-cannabinoid
made by plant Cannabis sativa

JWH-018: synthetic cannabinoid
made in chemistry laboratory

Anandamide: endocannabinoid
made by brain cells

Figure 4. Emerging designer hallucinogenic drugs: the rigid structures of the "flies"

Phenethylamine (PEA)

2C-Bfly

Br-Dragonfly

Table 1 – Page 1

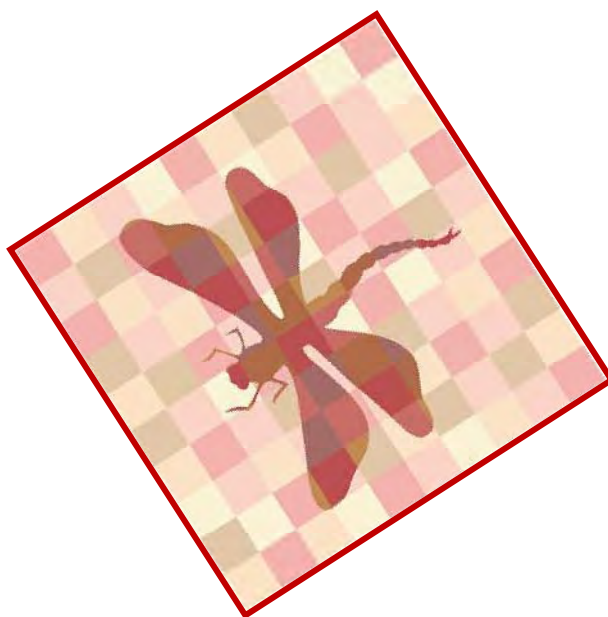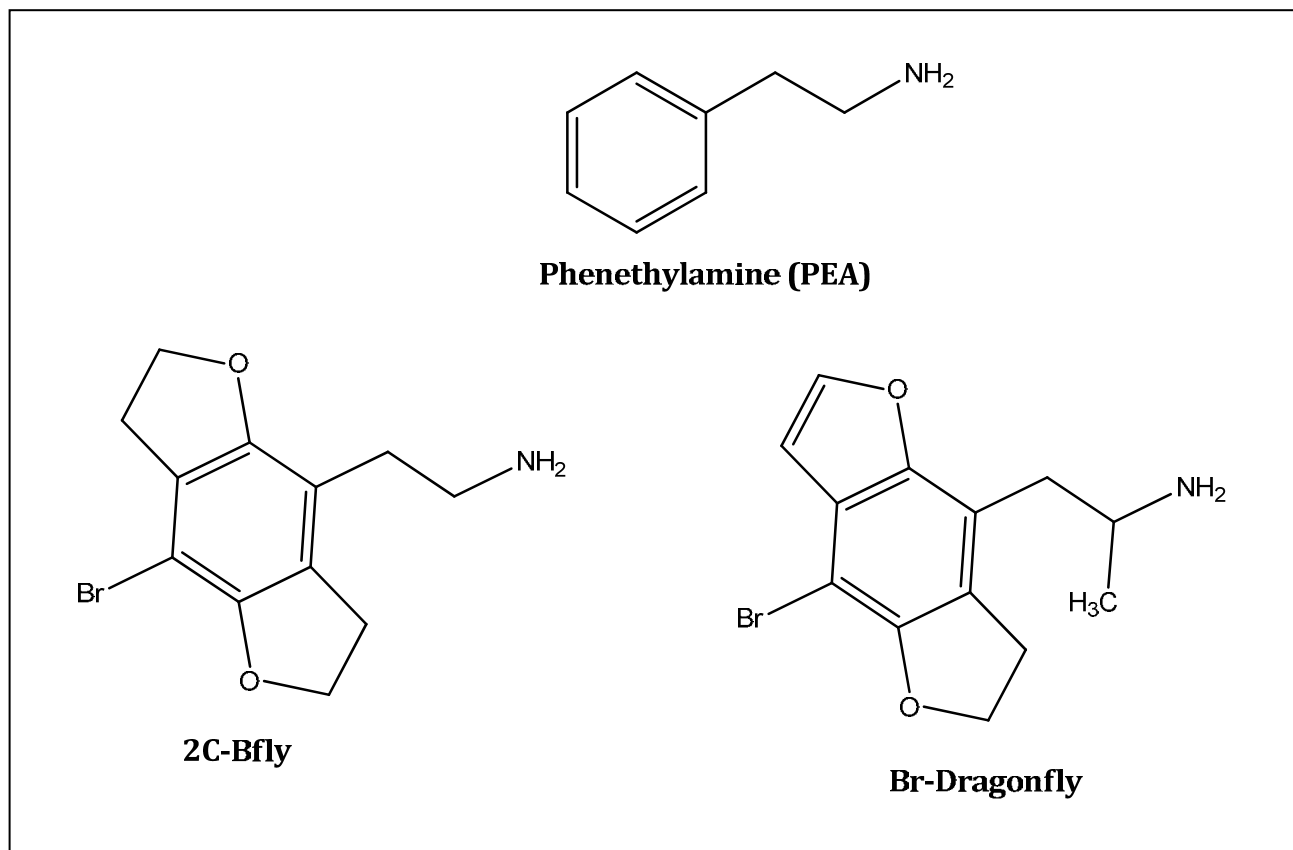|					
"Bath salts" (50-500 mg packets) Primary constituents: -MDPV (~5-20 mg+); -Mephedrone (500 mg-2 g/session); -Other cathinones: Butylone, methylone, Dimethylcathinone, ethcathinone, ethylone, 3-, or 4-fluoromethcathinone, Methcathinone, methdrone, ephedrone, pyrovalerone, naphyrone	Panic attacks, anxiety, agitations, paranoia, halucinations, psychosis, aggressive behavior, violence behavior, excited delirium, self-destructive behavior, self-mutilation, suicidal ideation, memory loss, insomnia, anorexia, depression, (Reviews: 18, 19, 20, 30-40, 50-61) Suspected Parkinson's disease (93)	tachycardia (rapid heart rate), hypertension (high blood pressure), vasoconstriction (blood vessel contraction), arrhythmias (irregular heart beat), hyperthermia (high temperature), sweating, pupil dilation, epistaxis (nose bleed), muscle tremor/spasms, hyper-reflexia (over responsive reflexes), rhabdomyolysis (muscle destruction), seizures, respiratory distress (breathing difficulty), myocardial infarction (heart attack), cardiovascular collapse (blood circulation failure), stroke (brain circulation failure), cerebral edema (brain swelling), coma, death (Reviews: 18, 19, 20, 30-40, 50-61, 64-66)	Unknown	> 1,500 mephedrone users surveyed considered it addictive (16) - of 100 mephedrone users nearly 50% reported continuous use for > 48 hours (26) -of 1,006 students, daily use reported by 4.4% (all less than 21 years old); 17.5% of users reported addiction (21)	-UK: High school and college students; 20% used on occasion; 4% used daily; all daily users under age 21 (21) -Finland: 8.6% of suspected DUI tested positive for MDPV. 84% were functionally impaired (18) -UK: 33% of club- goers used past month; 14% weekly; (20, 26)
"K2" or "Spice" Primary constituents:	Exacerbation of recurrent psychosis, psychosis relapse, new onset psychosis. Seizures	Tachycardia, tachyarrhythmia, cardiotoxicity, chest pain, nausea, vomiting, dilated	New onset psychosis, psychosis relapse; psychotic	Dependence (76)	-12th grade 11.4% (past) year (Monitoring the Future, 2011);

Table 1 – Page 2

JWH -018, JWH-073, JWH-200; HU-210; CP-47,497, others	Anxiety Agitation Irritability Memory changes Sedation Confusion Palpitations, compromised cognitive abilities (69-70; 73-75; 77-79)	pupils, brisk reflexes, appetite change, seizures, hot flushes, burning eyes, dilated pupils, drug mouth, tremors, myocardial infarction (76-70; 73-75)	episodes, anxiety, irritability (review: 69) Much remains unknown By analogy to marijuana, reduced brain volume,		-Ever use of "K2" reported by 8% of sample of college students (80)
Salvia Primary constituent: SalvinorinA					12th grade 5.9% (Monitoring the Future, 2011)
"Fly"		Death (88, 89)			
Methoxetamine, ketamine	Dissociative/catatonic state; Cerebellar toxicity (82-83, 85-86)	Tachycardia, hypertension (85); deaths (86)			
1,3-dimethylamylamine (DMAA)	Cerebral hemorrhage in 3 cases (81)				
"Whack" "Ivory Wave" 2-DPMP and D2PM	Agitation, anxiety, insomnia, psychosis, hallucinations, paranoia; in 26 cases, 96% had neuropsychiatric symptoms (84, 87)	Chest pain, hypertension, tachycardia, dystonia, rhabdomyolysis, (84)	Prolonged clinically significant neuropsychiatric symptoms (84)		1% past year use in night club survey (84)

Biography

Dr. Bertha K. Madras is Professor of Psychobiology, Department of Psychiatry at Harvard Medical School (HMS), and is cross-appointed at the Massachusetts General Hospital. She served as Deputy Director for Demand Reduction (prevention, intervention, treatment) in the White House Office of National Drug Control Policy (ONDCP), a Presidential appointment confirmed unanimously by the US Senate. At Harvard, her multidisciplinary research focuses on neuropsychiatric diseases and addiction biology, documented in over 150 manuscripts and as co-editor of books "The Cell Biology of Addiction", "Effects of Drugs in the Human Nervous System", "Imaging of the Human Brain in Health and Disease". At ONDCP, she incorporated Screening, Brief Intervention, Referral to Treatment (SBIRT) into the national drug control strategy, spearheaded SBIRT CPT®, other billing code approvals, Medicaid reimbursement, SBIRT adoption by Health Resources and Services Administration, the Veterans Administration, recruitment of Federal healthcare insurers, a UN declaration of endorsement, and other initiatives. In service to the public, she directed creation of a Museum exhibit, a CD (licensed by Disney Corp), "Changing your mind: drugs in the brain" for the Boston Museum of Science. She has given hundreds of presentations worldwide, on how drugs affect the brain and consults to government, organizations and industry. She holds 19 patents, is a recipient of a NIDA Public Service award, a NIH MERIT award, American Academy Addiction Psychiatry Founders' Award, and Marian Fischman Award. A brain imaging agent strategy she developed was cited by The Better World Report, 2006, as one of "25 technology transfer innovations that changed the world". Her experiences in translational neurobiology, government and public service afford her a unique perspective on science and public policy.

Conflict of Interest Statement

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

"Designer Drugs: An Escalating Public Health Challenge"

Signed electronically

Bertha K. Madras, PhD, September 10, 2012