REPORT 2 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (A-17)
Emerging Drugs of Abuse are a Public Health Threat
(Reference Committee E)

EXECUTIVE SUMMARY

Objective. Emerging drugs of abuse are a public health threat that needs actionable solutions from multiple stakeholders. Drug poisoning is the leading cause of injury death in the United States and drug poisoning deaths are at the highest level ever recorded. The Council on Science and Public Health initiated this report to bring attention to this public health issue and offer recommendations to address it.

Methods. English-language articles were selected from a search of the PubMed database through January 2017 using the search term "emerging drugs of abuse," coupled with "synthetic cannabinoid," "synthetic cathinone," "stimulant," "novel synthetic opioid," "fentanyl," "empathogen," "psychedelic," "dissociative," "depressant," and "public health;" and the search term "public health approach" in combination with "addiction" (not "gambling"), "substance misuse," and "drugs." Additional articles were identified from a review of the references cited in retrieved publications. Searches of selected medical specialty society and international, national, and local government agency websites were conducted to identify clinical guidelines, position statements, and reports.

Results. New psychoactive substances (NPS) are quickly emerging, transient, and difficult to track. Although some coordinated public health responses have been used to combat NPS outbreaks, most strategies and solutions to address illicit drug use remain compartmentalized and disconnected, and are lacking the necessary information and data sharing capability. A need for a multifaceted, collaborative multiagency approach to substance use exists. Increased NPS surveillance and early warning systems informed by laboratories and epidemiologic surveillance tools resulting in actionable information that can quickly reach law enforcement, public health officials, physicians, and vulnerable populations are solutions to mitigate the growing NPS problem.

Conclusion. The rate of NPS development and emergence is dramatically outpacing our ability to identify and regulate the compounds. Regulators agree that NPS will continue to pose a global threat to health and overdoses and deaths will continue to occur. Agreement also exists around the world that risks need to be highly publicized and education should be directed to correcting the perceptions that these substances are benign. Those who experiment with NPS have the ability to communicate and share experiences rapidly and globally using the Internet, which exacerbates the threat. Drug overdose deaths in the United States involving synthetic opioid drugs such as fentanyl and carfentanil have more than doubled between 2010 and 2015 and are expected to continue increasing. Continuing progress in eliminating the threat of NPS in the United States will require a comprehensive, multidisciplinary effort. Physicians, public health officials, law enforcement, first responders, and forensic laboratories all need to collaborate to decrease morbidity and mortality related to emerging drugs of abuse. Data systems need to be adaptable and utilized cooperatively by federal, state, and local agencies to derive actionable intelligence, and intelligence must be used in real-time to alert stakeholders of drug-related incidents. The frequent emergence of new NPS with unknown dangers and a potentially high death toll, especially NPS opioids, are a distinct challenge that will require a concerted and coordinated effort and response to mitigate risks to the public health and improve outcomes.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 2-A-17

Subject: Emerging Drugs of Abuse Are a Public Health Threat

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Referred to: Reference Committee E
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INTRODUCTION

"New psychoactive substance(s)" (NPS) refers to emerging designer drugs of abuse. The term was standardized by the United Nations Office on Drugs and Crime (UNODC) and is used by the U.S. Drug Enforcement Administration (DEA) and the enforcement agencies of other countries who monitor the development of such drugs.[1] A recent report from the UNODC confirms that NPS have become a phenomenon of transnational organized crime with a significant global impact; 102 countries have reported the emergence of NPS.[2] The ease of global e-commerce allows for anonymity and circumvention of law enforcement and public health controls.

The term "new" in NPS does not necessarily refer to novel chemical entities that have been newly synthesized; it also includes substances in existing pharmacological classes that are subject to abuse, but are not currently scheduled under international drug control conventions or federal or state statutes. For example, many NPS were designed as research tools or as candidates for drug approval that subsequently failed; synthetic pathways are often published in journals or found in patent applications. These compounds are ingested with the intent to mimic the effects of a wide range of psychoactive substances, including prescription opioids, cannabinoids, stimulants, hallucinogens, and central nervous system (CNS) depressants. NPS are sold as "legal highs" and alternatives to established drugs of abuse or as ways to "beat drug tests."[3] NPS may be 100 times more potent (or more) than existing pharmaceuticals but few, if any, have undergone formal pharmacological or toxicological testing.

Various classes of NPS have been associated with occurrences of adverse public health events around the United States. Heroin adulterated with the synthetic opioid carfentanil was linked to 174 opioid overdoses in six days in Cincinnati, Ohio.[4] Synthetic cannabinoids have been connected to the mass intoxication of individuals in a New York City neighborhood referred to as a "Zombie" outbreak.[5] With the increasing availability of NPS not only via the Internet, but in gas stations, convenience stores, adult stores, and smoke shops, effective prevention and treatment interventions will require broad cross-disciplinary approaches and cooperation among many stakeholders. The Council on Science and Public Health initiated this report to bring attention to this public health threat and offer recommendations to address it.

CURRENT AMA POLICY

AMA Policy H-95.940, "Addressing Emerging Trends in Illicit Drug Use," supports (1) assessing, monitoring, and disseminating information on emerging trends in illicit drug use; (2) developing

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continuing medical education on emerging drugs of abuse and; (3) expedited federal efforts to deem emerging drugs illegal. AMA policy recognizes substance use disorders, including addiction, as diseases and a public health hazard and supports a federal drug policy that is weighted more toward demand reduction rather than a law enforcement approach to address this problem (Policies H-95.976, H-95.975, H-95.981, H-95.983).

METHODS

English-language articles were selected from a search of the PubMed database through January 2017 using the search term "emerging drugs of abuse," coupled with "synthetic cannabinoid," "synthetic cathinone," "stimulant," "novel synthetic opioid," "fentanyl," "empathogen," "psychedelic," "dissociative," "depressant," and "public health;" and the search term "public health approach" in combination with "addiction" (not "gambling"), "substance misuse," and "drugs." Additional articles were identified from a review of the references cited in retrieved publications. Searches of selected medical specialty society and international, national, and local government agency websites were conducted to identify clinical guidelines, position statements, and reports.

NEW PSYCHOACTIVE SUBSTANCES (NPS)

NPS Regulation

NPS exist in a gray area between legal and illegal, and constitute an international policy challenge. A control framework has been developed by the UNODC to identify chemical classes, structural analogues, and specific substances that are prohibited from manufacture, distribution, and sale.[6-8] Establishing new controls in a timely manner is challenging because only a limited number of NPS have been reviewed and addressed by international drug convention members, each of which has their own national control regulations that may differ.

In early 2016, the European Union's European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) was monitoring more than 560 NPS, more than double the number of total drugs controlled under the UN conventions. In 2015, 100 of the compounds monitored by EMCDDA were detected for the first time, and more than 380 (70%) of those monitored were detected within the last 5 years.[1,9] In October 2015, the Chinese government controlled 116 new substances; carfentanil also is now a controlled substance in China.[10] The Japanese National Institutes of Health Sciences is a leader in surveying and identifying NPS; as of April 2015 Japan had scheduled 858 synthetic cannabinoids (SCs), making them illegal.[11,12]

In the United States, NPS are regulated using a rulemaking process under the Controlled Substances Act (CSA).[13] This rulemaking process can be initiated by United States Attorney General, at the request of the Secretary of the Department of Health and Human Services (HHS) with the concurrence of the U.S. Food and Drug Administration (FDA) and the National Institute on Drug Abuse (NIDA), or on the petition of any interested party. Most NPS are temporarily placed onto schedule I of the CSA when they are first properly determined to be biologically active and a threshold of data is obtained by the DEA. Temporary scheduling is effective for two years, which can be extended for an additional year if proceedings to permanently control the substance are initiated. After scientific and medical evaluation and a period of public comment, a final rule regarding substance scheduling can be issued. State policy makers have added specific chemicals and their analogues to their controlled substance schedules, and have created civil and criminal penalties that target NPS manufacturers and sellers.

Two standard approaches to identifying NPS for regulation exist in the United States. A neurochemical approach is used by the DEA, certain states (Iowa, Maryland, Texas), and other jurisdictions (District of Columbia). To assign a substance to schedule I using this approach, the substance must demonstrate receptor binding characteristics and be active in functional assays similar to an existing member of designated chemical classes. This approach theoretically eliminates the need to continually update schedules each time a new compound is discovered; it is limited to the binding site(s) recognized by the statute in each jurisdiction and by uncertainty about the level of proof necessary to satisfy the statutory requirement. The alternative method for regulation is the analogue approach, which requires that a substance be both substantially similar structurally to an existing Schedule I or II controlled substance, and that it has, or is intended to have, a substantially similar effect on the body as the scheduled substance. This approach covers every molecule as long as it is structurally similar to at least one schedule I or II substance. No clear guidance exists on what constitutes "substantially similar," and some substances have failed this test because of "lack of structural similarity," despite otherwise having the pharmacologic attributes of an NPS.[14] The legal and scientific communities recognize the need to clarify and simplify language around scheduling and also have identified a "language barrier" surrounding this issue as a challenge to overcome.

NPS Epidemiology

NPS usage is difficult to capture and is likely underreported because these drugs emerge quickly, may have a transient period of use, and are difficult to individually track and identify. Experts warn that because of the dynamic nature of the NPS market, many of the existing epidemiological indicators of drug use are poorly suited to measure or monitor the use of emerging substances. For example, including specific questions about the use of NPS in national surveys is difficult because these surveys often take years to plan and poison center data is often limited by the absence of analytical confirmation and reliance on secondary reporting of clinical features.[15]

NPS Pharmacology

Up to thirteen categories of NPS have been described by global authorities based on chemical structure.[1] Not all drugs in a chemical class produce the same pharmacological effects; for example, the phenethylamine category includes central nervous stimulants, d-lysergic acid diethylamide (LSD)-like hallucinogens, and 3,4-methylenedioxy-methamphetamine (MDMA)-like stimulant empathogen-entactogens (drugs that produce feelings of empathy, openness, and being touched). Furthermore, the same pharmacological effect can be produced by drugs from different categories; for example, many synthetic cathinones, substituted phenethylamines, and piperazines are central nervous system stimulants.

This report will focus on six broad categories based on pharmacological and clinical effects: synthetic opioids, synthetic cannabinoids, stimulants, hallucinogens (psychedelics and dissociatives), CNS depressants, and others (Table 1).

Synthetic Opioids. Serious adverse events, overdoses and deaths have been increasingly attributed to NPS opioids in recent years, the vast majority of which are fentanyl analogues (Table 1).[16-33] From 2014 to 2015, the death rate from synthetic opioids other than methadone increased by 72% in the United States, most likely illicitly manufactured fentanyl, and potentially other NPS opioids.[34] Fentanyl, its analogues, and other synthetic opioids are particularly concerning because they have recently been linked to numerous clusters of deaths around the United States. Carfentanil was linked to 174 opioid overdoses in six days in Cincinnati;[4] a cluster of deaths has been attributed to acetylfentanyl in Rhode Island;[35] illicit fentanyl has been marketed as cocaine

and resulted in an overdose cluster in Connecticut;[36] counterfeit Norco® (hydrocodone/acetaminophen) contaminated with fentanyl in Sacramento led to over 50 overdoses and 12 deaths;[37,38] and counterfeit Norco® in San Francisco (that was actually fentanyl and promethazine, which potentiates the CNS depressant effects of opioids) resulted in another public health threat.[39]

NPS synthetic opioids are generally selective mu-opioid receptor (MOR) agonists and former candidates for regulatory approval as therapeutic agents. The potency of these compounds varies greatly with some analogues having only slightly higher potency than morphine and others having significantly greater potency. For example U-47,700 is 7.5 times more potent, while carfentanil is 10,000 times more potent than morphine.[40-42] Knowledge about the majority of fentanyl analogues and other recent opioid-like NPS is limited because they have not been studied in humans. Even studying them in model systems is difficult because of their extraordinary potency which places researchers who handle them at high risk for harm from accidental exposure.[40]

China and Mexico are the primary source countries for many NPS opioids.[3,43-46] These compounds are being substituted for heroin and other opioids (such as hydrocodone), are being used to adulterate heroin and other non-opioid drugs of abuse, and are being sold on the street. Not only are they desired by those seeking relief from opioid withdrawal, they are gaining popularity as drugs of choice among recreational opioid users.[32,36] The DEA expects the designer NPS market, particularly designer fentanyls, to continue to expand as novel products attract new users.[3] In its 2016 annual Emerging Threat Report, 60% of the NPS opioids were identified for the first time.[47] Public warnings have been issued cautioning the public and law enforcement officials about the danger of the potency of NPS opioids and the fact that high or multiple doses of naloxone may be needed to reverse their effects in the event of an overdose.[36,44] A recent review details the structure-activity relationships of fentanyl-related compounds and derivatives,[48] which unregulated laboratories in China continue to develop.[49]

Synthetic Cannabinoids. SCs are the largest category among NPS and have become colloquially known by the names of previously "branded" products K2 and Spice (Table 1). SC products typically contain one or more compounds dissolved in a solvent and sprayed on a plant material, sometimes with flavorings such as bubblegum or strawberry, which is then smoked. The laced plant material is often placed in branded packets, labeled as "not for human consumption" in order to circumvent drug laws, and sold as "herbal incense."[3] These products also are being increasingly sold in liquid forms for e-cigarette cartridges.[3,50] The chemical structures of SCs vary greatly and new derivatives are emerging constantly. SCs have been associated with clusters of outbreaks of adverse events including severe delirium and "zombielike" altered mental status.[5,51,52]

A wide variety of SC chemical compounds exist that likely activate multiple pharmacological pathways causing diverse and unexpected adverse effects.[53,54] SCs are mainly cannabinoid receptor 1 (CB_1) agonists intended to mimic the effects of Δ^9-tetrahydrocannabinol (THC), however, some also have affinity for the peripheral cannabinoid receptor 2, CB_2.[54-56] Most SCs are full agonists, as opposed to the partial agonist activity of THC. They have higher affinity for cannabinoid receptors and act more rapidly at these receptors than does THC. Cannabis or cannabis plant extracts contain other cannabinioids including cannabidiol (CBD), which appears to possess anxiolytic or antipsychotic properties that can attenuate the psychotomimetic properties of THC. Because SCs exist in pure form, they generally result in more intense psychotomimetic effects than does use of herbal cannabis.[57] It is noteworthy that SCs are associated with severe psychosis, agitation, and intense sympathomimetic effects.[58] Additionally, many SCs have potent active metabolites which can cause prolonged adverse effects.[58] Considering the potency of the compounds, the risks of

misuse and addiction are a concern.[54] Recent reviews summarize structure-activity, epidemiology, pharmacodynamics, metabolism, clinical implications, and adverse effects of SCs.[12,55,58-63]

Stimulants. The category of NPS stimulants contains many classes of chemical structures with varying pharmacological effects and varying potency (Table 1). Convention has been to compare them to relatively well-studied stimulants.[64-66] Some compounds mimic amphetamine (classic psychostimulants) to produce arousal and stimulation. Others mimic MDMA ("Molly"), are empathogen-entactogens, and are used mainly to enhance sociability.[65] Still other NPS stimulants are intended to mimic cocaine or methylphenidate.[66-68]

A number of agents among the NPS stimulants commonly known as "bath salts" (usually synthetic cathinones) or "plant food" are sold as "research chemicals," and are labeled as "not for human consumption" in attempts to circumvent drug laws.[66] These chemicals are usually powders, crystalline mixtures, or pressed into tablets. Often NPS stimulants are mixed with cocaine or methamphetamine and many have become substitutes for MDMA, unbeknownst to users. Some common NPS stimulants in the news recently have been the different "bath salts," methylenedioxypyrovalerone (MDPV), mephedrone, and alpha-PVP ("Flakka").[69-71] It is not uncommon for users to be consuming multiple NPS stimulants in a product and to be unaware of the identity of the compound(s) they are using.

NPS stimulants alter synaptic concentrations of the neurotransmitters dopamine, norepinephrine, and 5-hydroxytryptamine (5-HT, otherwise known as serotonin) by inhibiting and/or inducing transport (reuptake) proteins to varying degrees.[65] The pharmacologic properties of NPS stimulants account for their potential to trigger patterns of misuse and addiction.[72] Adverse effects of NPS stimulants are reported to be similar to those of other stimulants.[65] However, their use may lead to serotonin syndrome, violence, homicidal combative behavior, self-mutilation, coma, and death.[64,66,73] Recent reviews summarize the neuropharmacology and adverse effects of NPS stimulants.[64,65,74,75]

Hallucinogens. Two distinct subcategories of NPS hallucinogens have emerged: psychedelics which are designed to have LSD-like activity, and dissociative agents which are purported to have phencyclidine (PCP) or ketamine-like pharmacologic effects (Table 1).

In addition to being LSD analogues, many NPS psychedelics are also members of the phenethylamine or tryptamine chemical classes and have multiple pharmacologic profiles. For example, some phenethylamines such as the NBOMe-series of drugs are stimulants as well as psychedelics.[64] This pharmacologic effect has been described as MDMA and LSD fusing together, thus producing new psychedelic substances.[76] NPS psychedelics generally affect extracellular serotonin concentrations.[64,65] As a result, serotonin syndrome and sympathomimetic toxicity are concerns.

Full pharmacologic profiles of many NPS psychedelics have not yet been elucidated; however, some analytical and animal model behavioral characterizations are beginning to emerge for individual compounds.[77,78] Receptor studies performed on individual NPS psychedelics reveal varied pharmacodynamic properties with respect to receptor affinity and activation of signaling pathways; drug users anecdotally recognize, respond to, and report on these differences.[64,79,80] A litany of over 230 psychedelic compounds, including synthesis instructions, bioassays, and dosages exists in two books, PiHKAL and TiHKAL, published by psychopharmacologist Alexander Shulgin (Shulgin is credited with discovering most of the cataloged psychedelic compounds).[81,82] Because the effects of these drugs vary dramatically, users can theoretically choose the experience they desire based on onset, duration, and relative potency to a compound such as LSD. Some of

these inherent properties lead to dangers; for example, in the case of Bromo-DragonFLY, very high potency coupled with delayed onset has resulted in re-dosing and subsequent toxicity.[83] Note that Shulgin has attained cult-hero status among users of these compounds; his books frequently glorify use of these products for recreational purposes – the neologism PiHKAL stands for "phenylethyamines I have known and loved," and TiHKAL stands for "tryptamines I have known and loved."

NPS dissociative drugs are primarily analogues of PCP and ketamine ("Special K") and as such are principally uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonists.[64,84,85] Many of the known PCP and ketamine analogues were developed through legitimate research and their structures exist in peer-reviewed and patent literature. However, re-emergence of NPS dissociative agents has occurred through online forums – with forum members collaboratively planning, synthesizing, and characterizing rationally designed compounds, including methoxetamine, with online "research chemical" vendors subsequently selling the compounds.[79,80,84] Little data on behavioral and psychological effects exist; however, anecdotal reports note effects comparable to PCP and ketamine although with varying degrees of intensity and duration.[86] Inconsistent data on withdrawal symptoms have been recorded; anecdotal reports of "cravings" have emerged.[64] Little toxicological data exist, although some case studies have been presented.[87] A recent publication reviews the non-medical use of dissociative drugs.[84]

CNS Depressants. NPS CNS depressants consist mainly of benzodiazepine analogues (Table 1). The first compounds to emerge as NPS benzodiazepines were phenazepam ("Bonsai") and etizolam. Because these drugs are controlled substances in a few European countries, entrepreneurs derived subsequent NPS from failed therapeutic drug candidates in old pharmaceutical research to circumvent drug laws in many countries.[88-90] Similar to marketed benzodiazepines, NPS benzodiazepines have active metabolites that are also marketed as NPS (for example, the active metabolite of flunitrazepam, norflunitrazepam, is marketed on drug forums as fonazepam). A diverse range of possible modifications and the potential for development of families of novel NPS benzodiazepines has public health officials concerned about this emerging class.[89] NPS benzodiazepines have been offered as research chemicals on the Internet; investigators and public health officials speculate these are consumed not only to induce a state of intoxication, but also for self-medication of anxiety disorders.[88]

Similar to classic benzodiazepines, NPS benzodiazepines bind to the ionotropic gamma-aminobutyric acid ($GABA_A$) receptor.[64,89] NPS benzodiazepines remain one of the least-well-characterized categories of NPS. Similarity to established agents is unclear; drug disposition and elimination rates are largely unknown, which takes on increasing importance in the context of multiple dosing, use by naïve patients, and/or use in combination with alcohol and other drugs. One study evaluated pharmacokinetic properties of a single dose of flubromazepam and noted a very long half-life of more than 100 hours and detectable urinary metabolites for more than 28 days post-ingestion;[91] the activity of metabolites was not assessed in this study. Also of note is that many of these compounds have a high potency compared to traditional benzodiazepines, which could lead to unintentional overdoses; there is also concern about their use in drug-facilitated crimes, including sexual assault and robbery.[92] Additionally, complex metabolic pathways and shared metabolites could complicate clinical investigation and analytical findings.

Others. Other emerging drugs (including botanicals and other classes of psychoactive drugs that do not fit neatly into the aforementioned categories) are being sold on the gray market and cataloged on online drug forums. Etaqualone, first synthesized in 1963, has become a popular "research chemical" for sale over the Internet and is watched by the DEA.[1,93] It is an analogue of

methaqualone (brand name Quaalude) and is a $GABA_A$ receptor agonist resulting in sedative and hypnotic effects. Several other methaqualone analogues cited in literature could emerge as NPS.[93]

Mitragyna speciosa is a deciduous tree indigenous to Thailand and other Southeast Asian countries. Over 25 alkaloids have been isolated from *M. speciosa* including mitragynine and 7-hydroxymitragynine, which are believed to be the primary pharmacologic constituents. Kratom is the colloquial name of the dried plant material of *M. speciosa.* Its active components are not classified as opioids but have been identified as partial MOR agonists and competitive kappa- and delta-opioid receptor antagonists.[94-96] *M. speciosa* leaves are often chewed fresh, but dried leaves in powder form are also available and are swallowed, brewed into a tea, or smoked. In low doses kratom is reported to have stimulant effects, while at high doses it can have sedative-narcotic effects. Kratom has been available for purchase as an herbal preparation, and there have been reports of adulteration of kratom products with O-desmethyltramadol and 7-hydroxymitragynine.[97,98] Traditionally *M. speciosa* has been used by Southeast Asian laborers to alleviate fatigue or as a mood enhancer and/or analgesic. More recently, in addition to recreational use, kratom has been touted as an antidepressant, anxiolytic, anti-inflammatory, analgesic, and alternative to methadone or buprenorphine for medication-assisted treatment of opioid use disorder.[94,95] Pharmacological studies evaluating kratom are limited, but are beginning to emerge.[99] The DEA recommended kratom for inclusion on schedule I of the CSA in early 2016, but public opposition led to reconsideration. The 8-factor analysis used in the decision not to add kratom to schedule I of the CSA concluded that kratom has substantially lower harmfulness and abuse potential than opioids and that its consumption is primarily motivated by its perceived benefits as a natural "home remedy" and alternative to conventional medicines for a variety of ailments.[95]

Ayahuasca is a brew of two plants, *Psychotria viridis*, which contains *N,N*-dimethyltryptamine (DMT), primarily a serotonin modulator, and *Banisteriopsis caapi*, which has monoamine oxidase inhibiting (MAOI) properties and is orally active.[100] Ayahuasca administration is characterized by a modified state of awareness where users experience deep introspection and increased insight, dream-like imagery, enhanced emotions, and recollection of personal memories.[100,101] Ayahuasca use originated as an Amazonian medicinal, spiritual, and cultural practice, but the experience has since spread into non-indigenous syncretistic and recreational practices worldwide. The globalization of ayahuasca has raised both public health and legal concerns.[102,103] Although DMT is on the UNODC international conventions scheduled list, no plants containing the drug are currently included on the list.[6-8] Some reports suggest that ayahuasca may have therapeutic effects for the treatment of substance use disorders and psychotherapeutic interventions.[101,104] Recent reviews discuss the pharmacology and therapeutic potentials of ayahuasca.[101,105]

Dietary supplements (DS) sold for weight-loss purposes are among the most adulterated DS on the market and are the third most prevalent group of supplements that require recalls of products containing unapproved pharmaceutical ingredients.[106] Several synthetic NPS stimulants have appeared in DS over the last several years, perhaps in an effort to replace Ephedra after it was banned.[107] Many are added to DS in the guise of a plant ingredient on the label. Some of the more noteworthy stimulants include the structurally similar 1,3-dimethylamylamine (DMAA) and 1,3-dimethylbutylamine (DMBA), which are labeled as geranium and Pouchong Tea, respectively, and have been associated with adverse health effects;[108-113] β-methylphenethylamine (BMPEA), often labeled *Acacia rigidula*, is the subject of an FDA study;[114,115] and N,α-diethyl-phenylethylamine (N,α-DEPEA), a methamphetamine analogue isomer which was labeled as dendrobium, has been the subject of several news stories.[116] A recent review discusses several NPS sympathomimetic stimulants that have been detected in DS.[107]

NPS MARKET

A UN World Drug Report on the world drug problem, published before a special session of the General Assembly, includes a detailed market analysis for each class of NPS; noteworthy are the numerous ways and forms in which they are marketed and the many different user groups engaged with NPS.[117] The UNODC and the DEA agree that the market for NPS will continue to expand and that the Internet is transforming the drug trade and allowing for global access to these emerging compounds.

Trafficking and selling NPS has a high profit margin. They are sold mostly on the surface Internet by major online marketplaces that advertise their products and accept payment by major credit and debit cards and online payment services or direct bank transfers through product websites. The anonymity, low-cost, scope, and apparent reliability of these websites makes it a challenge for law enforcement to seize the thousands of unmarked small packages being shipped to individuals all over the world. Research has been conducted detailing online cryptomarkets, the anonymous global Amazon-like marketplaces that seem to be a primary wholesale source of NPS on the deep web, and suggests likely growth in the coming years in sales and continued resilience to law enforcement.[118]

NPS TREATMENT CHALLENGES

NPS have been increasingly associated with hospital emergencies, acute adverse health consequences, and drug-induced deaths.[119] Individuals rarely know the dose and identity of the drug they are taking. Furthermore, other considerations include variable purity and potency of the active ingredient and the potential presence of adulterants or contaminants.

Treating NPS intoxication is limited by the lack of inexpensive and rapid screening tests to confirm the presence of most NPS. Very few, if any, NPS are detected by standard immunoassay urine drug screens, and with limited availability of reference standards, developing laboratory-validated analytical methods is a challenge. Even when analytical methods are developed, the rapid appearance of NPS on the market limits test reliability and the ability of laboratories to keep up. For individuals with histories suggestive of drug misuse, particularly opioids and benzodiazepines, physicians should be aware of this limitation and carefully assess “false-positive” urine drug testing results, much like medical review officer protocols advise.[32,92]

To add to these clinical challenges, some NPS (synthetic cannabinoids for example) have a short detection window in biological fluids, doses are low, the compounds are extensively metabolized, and little to no parent compound is excreted in urine.[12] Fentanyl and fentanyl analogues pose a threat not only to users, but also to health care professionals, law enforcement personnel, and postal service employees since minuscule amounts of the drug are lethal and can be inadvertently inhaled or absorbed through the skin.[3]

NPS AND PUBLIC HEALTH

Public health approaches have been used to successfully address outbreaks of NPS overdoses. When such approaches have been successful, pre-existing coordinated relationships among multiple groups (law enforcement, emergency medical services personnel, forensic laboratories, public health officials, social service providers, and hospital emergency department physicians and personnel) have allowed for a rapid and comprehensive response to a given outbreak and its sequelae.

For example, an extended pattern of SC use in Anchorage, Alaska was eventually contained through the use of multiple collaborative interventions.[51] In New York, New York, a "Zombie" outbreak caused by a new NPS was identified and characterized within 17 days, including the successful development of reference standards for the laboratory detection of emerging substances and their metabolites. This was made possible because of close collaboration among medical professionals who documented clinical histories, additional background and drug paraphernalia provided by law enforcement, and reliable analysis performed by laboratories.[5] Finally, a rapid and controlled public health response involving multiple health care providers reduced the impact of an outbreak of fentanyl laced cocaine in New Haven, Connecticut and mitigated more severe public health consequences.[36]

Although coordinated responses like the ones mentioned do exist, most strategies and solutions for illicit drugs remain compartmentalized and disconnected; examples of such surveillance programs are detailed below. A need for a multifaceted, collaborative multiagency approach to combat NPS use exists. This approach, as well as increased NPS surveillance and early warning systems informed by laboratories, and epidemiologic surveillance tools resulting in actionable information that can quickly reach law enforcement, public health officials, emergency physicians, and vulnerable populations will aid in mitigating the growing NPS problem.[34,120]

Surveillance

Public health and law enforcement agencies are both tasked with protecting individuals, but have different philosophies and use different methods. For example, the term "surveillance" in a public health context refers to systematic collection, analysis, interpretation, and dissemination of data regarding a health-related event; in law enforcement surveillance generally means the observation of people or premises during the course of an investigation. Recently, law enforcement entities have started to align their efforts more closely with public health objectives in an effort to combat the public health threat posed by emerging drugs of abuse.

The Council of State and Territorial Epidemiologists (CSTE) released a position statement in 2008 stating that the "identification and quantification of the determinants and human health consequences of use and abuse of substances is an essential first step in prevention."[121] At that time, substance abuse had no devoted categorization under the CSTE organizational structure and was not addressed in previous capacity assessments. The position statement called for the development of performance measures for addressing substance abuse within five years. In its 2013 National Assessment of Epidemiology Capacity, CSTE reported that less than 12 percent of states had substantial capacity for substance abuse epidemiology (by this time, a formal CSTE category), 43 percent of states had no capacity, and most states had no plans to develop capacity despite the fact that substance abuse problems contribute directly to the leading causes of death in the U.S. CSTE noted part of the reason for states' unwillingness to develop capacity in the area of substance abuse was "turf issues" with other agencies and a perception among politicians that treatment-based efforts are sufficient to combat the problem. CSTE recommends the development of a strategy to increase the epidemiologic capacity to address substance abuse at the local, state, and national levels and to encourage more effort to publicize successes and to expand the role of epidemiology in the program area.[122] Accordingly, in 2015, the SAMHSA Center for Behavioral Health Statistics and Quality (CBHSQ) incorporated a Community Epidemiology Team with deployment capacity to respond to local outbreaks related to drug use. In 2016, CBHSQ/SAMHSA began phase two of this project in partnership with CSTE to identify and promote a core set of behavioral health indicators intended to contribute to a national behavioral health surveillance system capable of responding to community-level needs. CSTE has a capacity assessment underway.

The National Drug Early Warning System (NDEWS) is funded by NIDA and administered by the Center for Substance Abuse Research (CESAR) at the University of Maryland. CESAR monitors emerging substance use trends. Its activities help enable health experts, researchers, and citizens to better respond to potential outbreaks of illicit drug use and to identify increased use of NPS.[123] NDEWS builds on what was formerly the NIDA Community Epidemiology Work Group (CEWG), monitoring not only local data from the CEWG program, but also incorporating a national perspective to monitor emerging issues.

Role of the DEA. In the United States, the DEA is tasked with identifying new drugs of abuse and determining the need to appropriately schedule and classify them in collaboration with the FDA and NIDA. Temporarily scheduling a new NPS by the DEA requires a threshold of data regarding that drug. In the current landscape of constantly emerging NPS, obtaining the relevant and appropriate amount of data from users who have experienced adverse events and overdoses can be challenging. Emergency department physicians are limited by drug testing capabilities at their facilities and may not collect appropriate specimens for testing and positive identification of NPS. Outbreaks may not be recognized, and medical examiner and coroner offices strained by increasing cases may not perform comprehensive toxicology screens on all cases and may miss NPS identifications. Additionally, reference materials may not be available in laboratories to identify new emerging compounds.

As new NPS emerge, the DEA collaborates with the Chemistry and Drug Metabolism Section (CDM) at NIDA. When data for regulation via the neurochemical approach are needed, CDM obtains purified drug samples from the DEA and performs the appropriate assays. The data obtained are quickly published to provide laboratories and regulating bodies around the world with needed information. The CDM also collaborates with universities worldwide and governmental forensic institutes, with the goal of circulating information to hospitals and laboratories as rapidly as possible and to share information about chemical structures with commercial reference standard manufacturers.[12]

The DEA Special Testing and Research Laboratory (STRL) has an Emerging Trends Program to analyze NPS for enforcement and intelligence purposes. However, a formal identification is made only when authenticated reference material is available for comparison. This is a limitation because many NPS may go undetected. When reference material is not available, the drug is identified as "substance unconfirmed." Throughout periods in the same calendar year, the landscape of drugs detected can change dramatically.[124,125] STRL also has a Reference Materials Program through which reference standards are synthesized and characterized. Information about NPS chemical structures are subsequently shared with law enforcement, forensic, and public health communities.

The DEA National Forensic Laboratory Information System (NFLIS) systematically collects results from federal, state, and local forensic laboratories to evaluate how substance use varies geographically. More than 300 state and local forensic laboratories in the United States exist, performing nearly two million drug analyses each year. The data in the most current yearly report include 50 state systems and 101 local or municipal laboratories/laboratory systems (representing a total of 277 individual laboratories) and federal data from DEA and U.S. Customs and Border Protection laboratories.[126] An NFLIS special publication on 2C-phenethylamines (mostly NPS stimulants and hallucinogens) reported a 295 percent increase in their identification from 2011 to 2015.[127] An NFLIS Brief reported a 15-fold increase in fentanyl reports submitted to laboratories between 2013 and 2015 and that the majority of fentanyl drug reports resulted from clandestinely produced and trafficked fentanyl, not fentanyl diverted from traditional pharmaceutical sources.[128]

Complications from emerging drugs of abuse, such as acetylfentanyl, frequently surface initially in emergency departments. Prompt recognition and treatment can help reduce morbidity and mortality. The American College of Emergency Physicians published an information paper highlighting the complexity of the NPS problem and providing a listing of surveillance sources for healthcare providers.[129] The National Drug Control Strategy recommends the pursuit of innovations in data collection that reach beyond traditional methods in an effort to keep up with the rapidly evolving drug culture. For example, scanning social media and using Internet search tools to understand local trends can augment local emergency department data, and technologies that estimate drug use within communities in real-time can complement traditional epidemiological survey studies.[10]

Fusion Centers

Data fusion involves the exchange and analysis of information, previously siloed, from multiple sources such as law enforcement, public safety, public health/health care, and the private sector, with the end goal of developing meaningful and actionable intelligence and information. Additionally, updates can be provided based on re-evaluation of data in the context of new information. Across the nation, fusion centers have been established to facilitate the sharing of information among multiple agencies and to build intelligence capabilities. It should be noted that fusion centers operate in accordance with existing state and federal privacy laws and requirements.[130-132] Both the Centers for Disease Control and Prevention (CDC) and the Association of State and Territorial Health Officials agree that reliable data are critical in order for public health and law enforcement agencies to effectively carry out their mission.[133] Because these organizations share a responsibility to protect the public, the CDC lists "information sharing" as one of the 15 capabilities for national public health preparedness standards that are used to assist public health departments in strategic planning.[134]

Generally, fusion centers have focused on bioterrorism, but their applications also include intelligence gathering and risk assessment for other hazards, including NPS, in order to protect the security of the country. Drug-specific fusion centers are being developed to better understand the scope of the drug problem in local communities and to enhance prevention, treatment, and enforcement efforts.

In New Jersey, the Drug Monitoring Initiative (DMI) is a successful example of a drug-specific fusion center.[135] The DMI was initiated by the NJ State Police in response to an exponential rise in drug overdoses. The goal is to better understand the scope of the problem through continuous statewide monitoring of drug activities. Continuous statewide monitoring of drug activities and creation of an "information sharing environment" enables law enforcement, community services, and public health experts to better understand trends, patterns, implications, and threats from illicit drug activity on both the supply and demand side. This process allows for intelligence-led policing, investigative support for law enforcement, and intelligence-led outreach for treatment and prevention efforts. DMI also has established a list of best practices, including a monthly conference call involving representatives from 48 states in order to provide information to other law enforcement, public health, and fusion centers across the country. Additionally, a basic drug recognition course is offered for law enforcement first responders and health partners so they are informed about emerging drug trends and able to share the information. Four additional sites in the United States are currently being modeled after DMI. See Appendix 1 for a summary sheet outlining the DMI program.

Interventions Directed at Preventing or Reducing Harm

Educational campaigns are effective at reducing harms from NPS.[136] Drug checking is another harm reduction strategy utilized by drug users to evaluate the contents of pills or powders after obtaining them. Some users will seek illicit drugs despite the known risks of substitution and adulteration, for example as with MDMA. The availability of commercially available kits allows users to distinguish MDMA from other compounds, such as bath salts, before use. Commercially available drug checking kits, although limited by the methods used to check the drugs, are an effective strategy to test contents of pills and powders for validity and/or the addition of contaminants or adulterants. The rationale is that if prevention campaigns have failed, this harm reduction strategy could result in more informed user decisions.[119,137]

CONCLUSIONS

The rate of NPS development and emergence is dramatically outpacing our ability to identify and regulate such substances. The UNODC and the DEA agree that NPS will continue to pose a global threat to health, and overdoses, other serious adverse events, and deaths will continue to occur. Agreement also exists around the world that risks need to be highly publicized and education should be directed to correcting the perceptions that these substances are benign. Those who experiment with NPS have the ability to communicate and share experiences rapidly and globally using the Internet. As an example, the chemistry and subjective effects of the SCs contained in "Spice" products were being discussed by users in online forums at least 2 years before they were officially identified and characterized by a laboratory.[138] Drug overdose deaths in the United States involving synthetic opioid drugs such as fentanyl and carfentanil have more than doubled between 2010 and 2015 and are expected to continue increasing.[139] Continuing progress in eliminating the threat of NPS in the United States will require a comprehensive, multidisciplinary effort. Physicians, public health officials, law enforcement, first responders, and forensic laboratories all need to collaborate to decrease morbidity and mortality related to emerging drugs of abuse. Data systems need to be adaptable and utilized cooperatively by federal, state, and local agencies to derive actionable intelligence, and intelligence must be used in real-time to alert stakeholders of drug-related incidents. The frequent emergence of new NPS with unknown dangers and high death tolls, especially NPS opioids, are a distinct challenge that will require a concerted and coordinated effort and response to improve outcomes.

RECOMMENDATIONS

The Council on Science and Public Health recommends that the following be adopted and the remainder of the report be filed:

1. That Policy H-95.940, "Addressing Emerging Trends in Illicit Drug Use," be amended by addition and deletion as follows:

   Addressing Emerging Trends in Illicit Drug Use
   Our AMA: (1) recognizes that emerging drugs of abuse, especially new psychoactive substances (NPS), are a public health threat;

   ~~(1)~~ (2) supports ongoing efforts of the National Institute on Drug Abuse, the Drug Enforcement Administration, the Centers for Disease Control and Prevention, the Department of Justice, the Department of Homeland Security, state departments of health, and poison control centers to assess and monitor emerging trends in illicit drug use, and to develop and disseminate fact sheets, ~~and~~ other educational materials, and public awareness campaigns;

(3) supports a collaborative, multiagency approach to addressing emerging drugs of abuse, including information and data sharing, increased epidemiological surveillance, early warning systems informed by laboratories and epidemiologic surveillance tools, and population driven real-time social media resulting in actionable information to reach stakeholders;

(4) encourages adequate federal and state funding of agencies tasked with addressing the emerging drug of abuse health threat;

~~(2)~~ (5) encourages the development of continuing medical education on emerging trends in illicit drug use; and ~~(3)~~

(6) supports efforts by ~~the~~ federal, state, and local government agencies to identify new drugs of abuse and to institute the necessary administrative or legislative actions to deem such drugs illegal in an expedited manner. (Modify Current HOD policy)

2. That our AMA participate as a stakeholder in a CDC/DEA taskforce for the development of a national forum for discussion of NPS-related issues. (Directive to Take Action)

Fiscal Note: $1,000

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Table 1. New psychoactive substance opioids, synthetic cannabinoids, stimulants, hallucinogens, CNS depressants, and other substances.[48,55,64,65,84,89]

	Opioids	Synthetic Cannabinoids	Stimulants	Hallucinogens	CNS Depressants	Others
Sub-category			Synthetic Cathinones (amphetamine-like)[1] Empathogen-entactogens (MDMA-like)[2] Methylphenidate-like[3] Cocaine-like[4]	Psychedelics (LSD-like)[5] Dissociatives (PCP-like)[6]	Benzodiazepine-like	Plants/Extracts[7]
Selected Examples	Acetylfentanyl Acryloylfentanyl AH-7912 Butyr-Fentanyl Carfentanil Furanyl Fentanyl MT-45 Ocfentanil U-47,700 U-50488 W-15 W-18	5F-ADB-PINACA 5F-PB22 ADB-FUBINACA AM-2201 CP-47,497 FUB-NPB-22 FUB-PB-22 HU-210 JWH-018 JWH-201 JWH-370 NNEI RCS-4 UR-144 XLR-11	2-DPMP[3] 3-FMC[1] 5-APB[2] 6-APB[2] Alpha-PVP[1] Butylone[1] BZP[1] Ethylphenidate[3] Flephedrone[1] m-CPP[2] MDAI[2] MDPV[1] Mephedrone[1,2] Methcathinone[1] Methylone[1,2] Naphyrone[1] PMA[1,2] RTI-111[4] TFMPP[2]	"Fly" drugs (Bromo-dragonfly)[5] 1P-LSD[5] 2C-series[1,5] 2-MeO-diphenidine[6] 2-MK[6] 3-MeO-PCE[6] 3-MeO-PCPy[6] 4-MeO-PCP[6] 5-MeO-Dalt[5] AMT[5] Diphenidine[6] DiPT[5] DMT[5] Ephenidine[6] LSZ[5] Methoxetamine[6] Methoxydine[6] NBOMe series[1,5] N-EK[6]	3-Hydroxyphenazepam 4'-Chlorodiazepam Adinazolam Bromazolam Clonazolam Cloniprazepam Deschloroetizolam Diclazepam Etizolam Flubromazepam Flubromazolam Fonazepam Iso-flubromazepam Meclonazepam Metizolam Nifoxipam Nitrazolam Phenazepam Pyrazolam	Ayahuasca[7] *Catha edulis* (Khat)[7] Etaqualone Kratom (mitragynine)[7]
Common Street Names		Black Mamba Crazy Clown K2 Scooby Snax Spice	Bath Salts Flakka Meow Meow Sextacy (MDPV) Vanilla Sky	Benzo Fury Cimbi-5 N-bomb (NBOMe-series) Smiles	Bonsai	
Site(s) of action	MOR (primarily)	CB_1 and CB_2	NET, DAT, SERT	5-HT GPCRs[5]	$GABA_A$ Receptor	Various
Mechanism(s) of Action	Agonist	Full receptor agonists Active metabolites	Inhibit MOA reuptake transporters and increase amount of NT present; Ratio of NTs present influences drug action	NMDA Receptor[6] Agonism or partial agonism of 5-HT_{2A}, agonism of 5-HT_{2C} and 5-HT_{1A}[5] Uncompetitive antagonists[6]	Agonist	Various

MDMA, 3,4-methylenedioxy-methamphetamine; LSD, d-lysergic acid diethylamide; PCP, phencyclidine; MOR, mu-opioid receptor; CB_1, cannabinoid receptor 1; CB_2, cannabinoid receptor 2; NET, norepinephrine transporter; DAT, dopamine transporter; SERT, serotonin transporter; MOA, monoamine; NT, neurotransmitter; 5-HT, serotonin; GPCR, G-Protein coupled receptor; NMDA, N-methyl-D-aspartate; $GABA_A$, gamma-aminobutyric acid

Appendix 1: Overview of the New Jersey Drug Monitoring Initiative (DMI).

An Intelligence Capability to Understand New Jersey's Drug Environment

Drug Monitoring Initiative (DMI) Overview

Heroin and opiate use in New Jersey has increased exponentially in recent years. The high rate of addiction drives the increased demand for both heroin and prescription painkillers, and recent statistics identify an increase in illicit heroin and opiate use, seizures, and deaths. During 2013, the State Medical Examiner's Office recorded 1,336 fatal drug overdoses. This common scenario has indiscriminately played out in New Jersey and across the country, affecting all races, genders, age groups, and social classes.

The New Jersey State Police developed DMI in response to this situation and to understand the scope of the problem through continuous monitoring of drug activity statewide. The DMI intelligence capability establishes a drug information sharing environment that enables law enforcement, human services, and public health experts to better understand trends, patterns, implications, and threats from illicit drug activity having an impact on specific locations statewide. DMI gathers investigative and administrative data, both on the supply side and the demand side, to develop a 360-degree view of the State's drug environment. The analysis is used to produce intelligence products for partners across state and local agencies and non-profit organizations. This process enables intelligence-led policing and investigative support for law enforcement and intelligence-led outreach for treatment and prevention efforts.

Collection Process

Various agencies collect drug data needed to interpret New Jersey's illicit drug environment. DMI leverages the existing people, processes, and platforms through an information sharing network which directs essential drug data sets to DMI for storage, analysis, production, and sharing. DMI leverages the following entities, which provide the respective data elements through data-sharing agreements and in a de-identified fashion, where appropriate:

- State Police and county forensic laboratories – all analyzed drug data
- NJ Department of Health (DOH) – EMS Narcan deployments
- County Prosecutor's Offices – Narcan deployments by law enforcement
- State Medical Examiner's Office – Drug involved death data
- NJ Mental Health and Addiction Services – Patient admissions and drug use data
- Automated Fingerprint Information System – Daily drug arrest data
- Prescription Drug Monitoring Program – Collected transactional data

Production

All of the information allowed to be shared is normalized and uploaded to the Project Safe Neighborhood Mapping Program, where it is stored, geo-coded, mapped, and made available to law enforcement, human services, and health partners via MAGLOCLEN's RissNet portal. DMI analysts use this information to provide:

1) Investigative support for strict liability cases and other drug investigations.
2) Situational awareness through the following products:
   - Daily Drug Environment Report – Heroin stamps seized and involved in overdoses are included in this report along with opiate pills seized in NJ.
   - Ad hoc Alerts – The NJ ROIC provides heroin overdose alerts, new and emerging drug notifications, and drug environment products from New Jersey and other regional DMI partners.

Training and Outreach

To increase drug awareness and information sharing, DMI developed the:

1) Monthly Conference Call – Brings together law enforcement, health partners, fusion centers and other entities to share information pertaining to drug trends in different areas of the country.
2) Basic Drug Recognition Course – Law enforcement, fire service, EMS, and health partners learn about drugs, trends, identifiers, and how to collect and share drug-related information.

DMI Established Best Practices

- Facilitates collaboration among diverse multidisciplinary entities to address the drug problem
- Uses automated drug data collection processes to ensure a timely exchange of information
- Desensitizes information to ensure seamless and transparent information sharing
- Derives intelligence from all investigative and administrative drug data
- Incorporates subject matter experts from various disciplines into the drug intelligence production process
- Supports narcotic investigations and overdose strict liability cases
- Employs the Journey-to-Drugs methodology to understand a drug's impact on local areas
- Coordinates collection, analysis, and mapping of drug-incident data statewide
- Facilitates expedited analysis of drugs seized through forensic labs
- Uses empirical data as opposed to survey data to understand the drug environment
- Provides drug training for law enforcement, fire service, and EMS personnel
- Provides drug situational awareness for all constituents
- Tracks Naloxone administrations by law enforcement and EMS statewide to identify potential spikes in drug overdoses
- Provides real time alerts to the public, law enforcement, and healthcare partners of spikes in drug overdoses occurring in specific areas
- Creates & leverages a network of existing people, platforms, and processes

For more information on the Drug Monitoring Initiative, contact Sgt. Adam Polhemus at lpp6422@gw.nsjp.org or call 609-414-3356.