Abstract:

Illicit drug use by adolescents is an old problem with new clinical challenges, as teens access synthetic drugs in schools, on the street, and through internet purchase. Detection of synthetic drugs and unknown adulterants is often impossible using standard drug screens, but may be identified with the assistance of regional poison centers and the forensic laboratories of local universities and law enforcement, including the Drug Enforcement Agency. While clinical care for most intoxication and overdose cases is still largely supportive, critical interventions may be necessary for some. Toxicology experts at poison centers not only provide management advice contemporaneous to care, but compile data to identify local dangerous drug activity. This article reviews current knowledge of synthetic cannabinoids, amphetamines, and opioids, as well as the increasing teen use of "vaping" devices for delivery of tobacco and other substances.

Keywords:

illicit drug use; synthetic cannabinoids; synthetic amphetamines; synthetic opioids; vaping; poison center

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Adolescents and Drug Abuse: 21st Century Synthetic Substances

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Adolescent drug abuse is a common problem worldwide. In the 15- to 24-year-old age group in the United States, intentional and unintentional poisonings are the second leading cause of injury and death, accounting for approximately 5700 deaths in 2016.[1] However, the annual prevalence of all illicit drug use (exempting marijuana) has been declining in the United States among teens, from a high of 30% in the late 1990s, to 13% among 12th graders in 2017. Lifetime prevalence of any illicit drug abuse (exempting marijuana) in the same group was 20% in 2017. In contrast, annual use of marijuana among 12th graders in 2017 was nearly 40% and has been on the rise since 2006.[2]

A "honeymoon period" for a new drug has been described. This period occurs when an illicit drug becomes available, supposed benefits of the drug are spread by word of mouth, Internet, and social media, and drug use rises. In contrast, information about adverse effects takes longer to disseminate, as this evidence is not immediately apparent. The use of e-cigarettes and vaping may currently be in this "honeymoon period."[2] Synthetic cannabinoids and "bath salts" may have been subject to this phenomenon as well.

Following an illustrative case, this article will review what is known about synthetic cannabinoids, amphetamines, and opioids, and the practice of "vaping." Acquisition by adolescents of the all the substances described here is often facilitated by use of the Internet. For a short time, loopholes in US drug laws allowed sales of synthetic cathinones and synthetic cannabinoids, all

legally purchased at stores, "head shops," or via the Internet. These drugs were collectively called "legal highs." A common disclaimer on packaging was the phrase "not intended for human consumption," labeled to circumvent the Federal Analog Act, a section of the US Controlled Substances Act. Currently, many synthetic drugs of abuse can easily be acquired online through the "darknet," or the deliberately hidden portions of the Internet accessed only with software that guarantees encryption and anonymity.

CASE

A 15-year-old male adolescent was found unresponsive at a teen house party and 911 was called. His friends reported to EMS that he used "acid," and medics witnessed a generalized tonic clonic seizure en route to the hospital. His initial vital signs included a temperature of 38.6°C, heart rate 151 beats per minute, and blood pressure 194/85 mmHg. He arrived to the emergency department (ED) unresponsive with mydriasis, and no evidence of trauma. Family members reported no past medical or surgical history. Laboratory data revealed a normal blood glucose, a peripheral WBC of 20 000, and profound acidosis, with a pH of 6.6 on a venous blood gas. His noninfused brain computerized tomography (CT) scan was negative for acute intracranial bleed or injury, the electrocardiogram (ECG) demonstrated sinus tachycardia and no other abnormalities, and the urine drug screen was positive for tetrahydrocannabinol (THC). He was intubated and admitted to the pediatric intensive care unit (PICU).

Synthetic Cannabinoids

Synthetic cannabinoids compromise a large group of compounds that are cannabinoid-receptor agonists. Common street names include "K2," "spice," "black mamba," "blaze," "smoke," and "skunk." The first compounds were synthesized in the 1980s for research purposes. Early on, synthetic cannabinoids were often marketed and sold as herbal incense. Abuse of these substances became more widespread in the US around the 2000s. First-generation synthetic cannabinoids included compounds named JWH-018, JWH-073, and JWH-250. Newer generation synthetic cannabinoids include a diverse family of molecules with names such as FUB-AMB, 5F-ADB. FUB-AMB was the most common synthetic cannabinoid identified in drug seizures by the Drug Enforcement Agency (DEA) in 2017 and the first half of 2018. 5F-EDMB-PINACA and 5F-MMB-PICA were identified for the first time in Drug Enforcement Agency (DEA) drug seizures in 2018.[3] The original compound was dissolved in solvents and applied to dry plant material. They compounds are almost exclusively smoked. The annual prevalence of use of synthetic cannabinoids among US 12th graders was reported as 11.3% in 2012, declining to 3.7% by 2017.[2] Mass outbreaks continue to be reported throughout the United States, including in Florida,[4] Connecticut, and New York City.[5] These cases were initially reported in a sensational manner, with headlines of "zombie" outbreaks.[5] It has yet to be seen how the increasing availability of legal recreational and medical marijuana will affect the abuse of synthetic cannabinoids.

Review of synthetic cannabinoid intoxications and adverse effects showed that tachycardia, agitation, and nausea were the most common signs and symptoms. Typical length of stay in the hospital or ED was less than 8 hours although it is possible these results were skewed towards cases of *first-generation* synthetic cannabinoids.[6] Newer generations of synthetic cannabinoids have more serious effects and higher morbidity, resulting in longer duration of observation and medical care. Case reports include cerebral vascular accidents, cardiotoxicity, including myocardial infarction,[7,8] bradycardia,[9] acute kidney injury,[10] hepatotoxicity,[11] and seizures. Patients with acute kidney injury typically presented with nausea, vomiting, and flank or abdominal pain. In addition, altered mental status in the form of "zombie-like" behavior has been seen. Patients were described as slow to respond, staring, with intermittent "zombie-like" groaning, and mechanical movement of extremities. These behaviors normalized in 9 hours.[5] Confusion, disorientation, and slurred speech were seen more commonly with synthetic cannabinoids when compared to marijuana.[12] Also, psychosis and bizarre behavior was much more common with synthetic products when compared to marijuana.[13] It is speculated that Sativa, one of the many other cannabinoids besides THC found in cannabis, may have antipsychotic activities, mitigating the appearance of "psychotic" behaviors and physical findings.

Laboratory evaluation of any patient should be individually tailored. The standard urine drug screen is unlikely to detect any of these synthetic cannabinoids. It may be this property, the failure of detection, which drives the continued abuse of synthetic cannabinoids by adolescents despite increased availability of marijuana.[14] Laboratory evaluation of a minimally symptomatic patient will have limited yield for isolated synthetic cannabinoid use. However, in a patient with altered mental status

or behavior, or seeking to hide his/her drug use, it is important to consider the historian unreliable. Despite an initial clinical suspicion of illicit drug use, the diagnostic differential remains wide, with alternate diagnoses informing diagnostic testing.

A teen presenting with altered mental status requires an immediate glucose check, vital signs, cardiac rhythm assessment, pulse oximetry and end-tidal carbon dioxide monitoring, all concomitant with a thorough head-to-toe examination. The medical work-up is informed by: (1) history, provided by family, friends, other peers, and any eye-witness to patient activity in the period just prior to illness, and (2) physical exam, with a search for findings indicative of drug intoxication, medical illness, and traumatic injury. The following may be useful in establishing a diagnosis: serum alcohol level, aspirin and acetaminophen levels, comprehensive metabolic analysis with attention to the presence of an osmolar or anion gap, CT brain imaging, ECG and cardiac enzyme analysis, blood gas analysis with attention to methemoglobin and carboxyhemoglobin levels, thyroid testing, and in some cases, cerebrospinal fluid analysis.

Treatment is entirely supportive for synthetic cannabinoid intoxication. No direct antidote exists. Airway control may be needed in more severe cases. Benzodiazepines should be the first-line treatment for agitation. Seizures should also be treated with benzodiazepines. Traditional antiepileptic drugs, such as phenytoin and carbamazepine, are unlikely to be of benefit. Antiemetics may be used for nausea and vomiting.

There is limited data regarding treatment for acute myocardial infarction (AMI) in the setting of teen use of synthetic cannabinoids and/or other illicit drugs. However, treatment for AMI should proceed in a standard manner with the involvement of a cardiologist. Evaluation and treatment may include anticoagulation, serial cardiac enzyme analysis and ECGs, other cardiac imaging, and, if the patient meets standard criteria, cardiac catheterization with reperfusion techniques. ✚

SYNTHETIC AMPHETAMINES

Amphetamines are substituted phenethylamines and share structural similarity to endogenous compounds, including dopamine and adrenaline. Numerous amphetamine analogs exist and have similar effects in patients who abuse amphetamine.

Cathinone and synthetic cathinones are one type of amphetamine analogs. Cathinone is a naturally occurring compound found in a plant called Khat (*Catha edulis*), native to Africa and the Arabian Peninsula, often used in these regions as a natural stimulant. Cathinone is a Schedule I controlled substance in the United States. Synthetic cathinones are compounds derived from the cathinone molecule. Many were first synthesized in the early 20th century but they emerged worldwide as a drug of abuse in the late 2000s, reaching near-epidemic proportions in the US in late 2010. Synthetic cathinones are colloquially known as "bath salts," and were often marketed as such or as "plant food." The original common synthetic cathinones include mephedrone, methylone, methcathinone, and MDPV (methylenedioxypyrovalerone). Newer compounds have since emerged. N-ethylpentylone was the most commonly identified cathinone in DEA drug seizures in 2017. More recently, N-ethylhexedrone was identified in 2018. Bath salts were marketed under many names, including "ivory wave," "vanilla sky," "bliss," and "meow meow." They generally appear as a white powder and are usually inhaled, but can be taken orally, smoked, or injected. Annual bath salt use among 12th graders in the US is low, reported at 1.1% in 2013.[15]

Synthetic amphetamines exist as large families of molecules and all are derived from the phenethylamine molecule. Substitutions at various positions produce new molecules and novel compounds (see Figure 1). For example, "2C-B" is 4-bromo-2,5-dimethoxyphenethylamine, "2C-C" is 4-chloro-2,5-dimethoxyphenethylamine, and "2C-D" is 4-methyl-2,5-dimethoxyphenethylamine. Other synthetic amphetamines include 25i-NBOMe (commonly known as "N-Bomb"), alpha-PVP (commonly known as "gravel" or "flakka"),[16] and paramethoxymethamphetamine (PMMA) and paramethoxyamphetamine (PMA). PMA and PMMA were responsible for a recent cluster of deaths in Canada after being mistaken by users for 3,4-Methylenedioxymethamphetamine (MDMA).[17]

The physical effects of synthetic amphetamine analogs are similar to those with amphetamine or methamphetamine intoxication, producing the sympathomimetic toxidrome. Patients may present with mydriasis, diaphoresis, pallor, agitation, tachycardia, hyperthermia, hypertension, and seizures. Refer to Table 1 for this toxidrome, which can be remembered using the "MD PATHS" acronym. More severe signs include aggressiveness, combative behavior, life-threatening agitation, and excited delirium syndrome. As a part of the sympathomimetic toxidrome, chest pain and myocardial infarction have occurred, as well as metabolic acidosis, rhabdomyolysis, seizures, and multi-organ failure. Hyperthermia is an ominous clinical finding, associated with significant risk for morbidity and death.

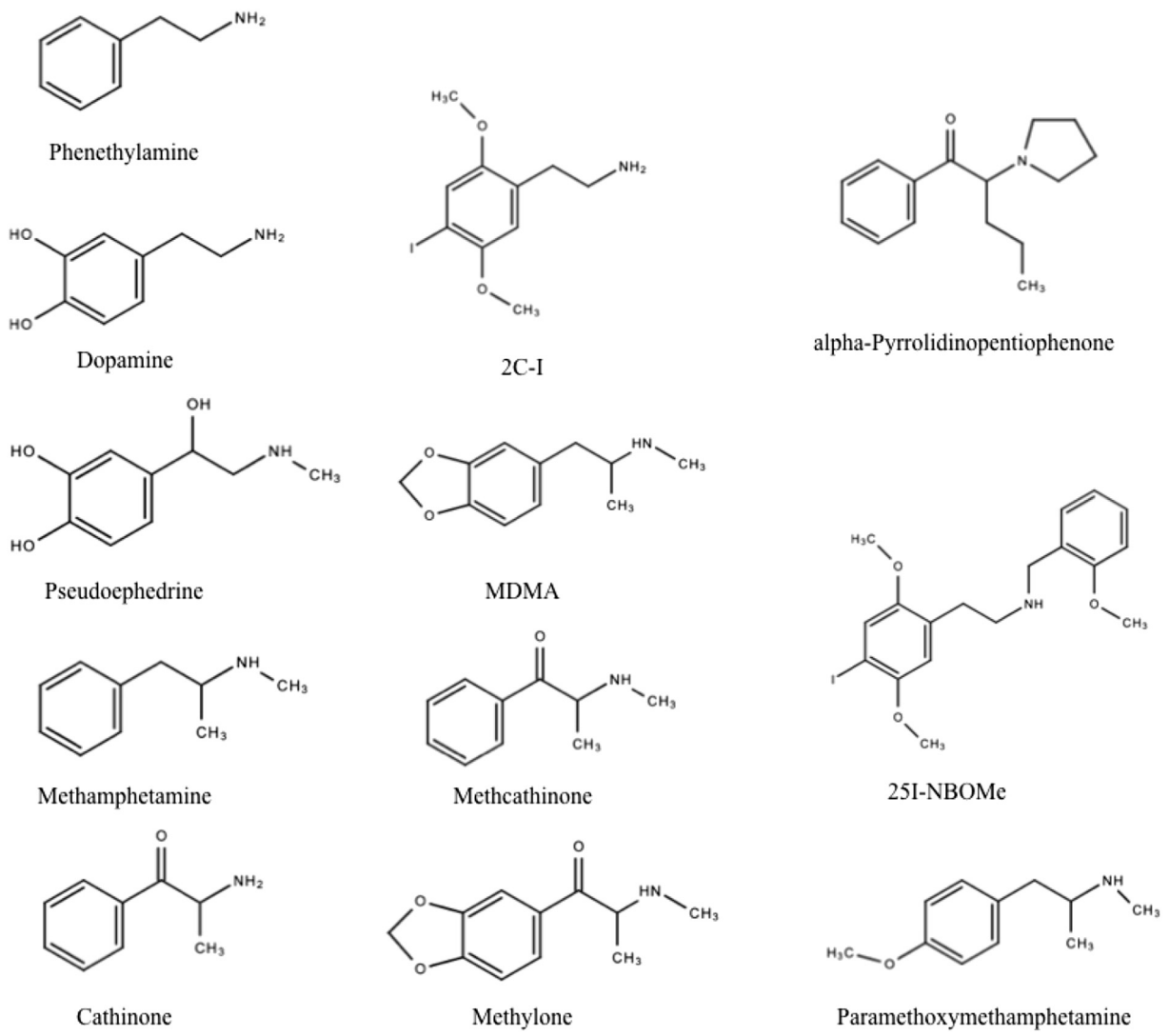

Figure 1. Synthetic amphetamines exist as large families of molecules, all derived from the phenethylamine molecule. Substitutions at various positions produce novel compounds.

TABLE 1. Signs of sympathomimetic intoxication using the "MD PATHS" acronym for this toxidrome.

	Sympathomimetic toxidrome
M	Mydriasis
D	Diaphoresis
P	Pallor
A	Agitation
T	Tachycardia
H	Hyperthermia, hypertension
S	Seizures

Similar to synthetic cannabinoids, none of these compounds would be expected to produce a "positive" result on a standard urine drug screen. Laboratory evaluation of any patient should be individually tailored, with symptomatic patients requiring more work-up in consideration of alternative medical diagnoses.

Treatment is entirely supportive, consistent with any sympathomimetic poisoning. No direct antidote exists. Sedation with benzodiazepines should be first-line treatment and benzodiazepines as monotherapy can often effectively treat agitation, tachycardia, and hypertension in most patients. Standard doses of benzodiazepines may not be sufficient, with recommendations for aggressive dosing in the severely agitated patient. Maintaining adequate

oxygenation and ventilation may require intubation and definitive airway control in the setting of severe toxicity. Antipsychotics (both typical and atypical) have also been successfully used to treat agitation. Intramuscular ketamine has been successfully used to treat cases of excited delirium as well.[18] Hypertension often does not need an antihypertensive medication, due to the sedating effects of benzodiazepine treatment. However, if there is evidence of end-organ compromise due to hypertension and an anti-hypertensive is considered, beta blockers should be avoided, as the resultant unopposed alpha activity is dangerous in the setting of sympathomimetic poisoning. Hyperthermia should be aggressively treated with active cooling measures. Antipyretics would not be expected to have any effect. Neuromuscular paralysis can be used in a patient with refractory sympathomimetic effects.

SYNTHETIC OPIOIDS

Synthetic opioids have become common adulterants in the illicit drug supply as a substitute for heroin. Fentanyl, with a potency 100 times that of morphine, is a Schedule II synthetic opioid and the most common synthetic opioid isolated in drug seizures by the DEA. The National Forensic Laboratory Information System (NFLIS) demonstrated a dramatic increase in fentanyl reporting beginning in 2014, with simultaneous steady decline in reports of oxycodone and hydrocodone use. Illicitly produced fentanyl can be found in tablet form, often made to resemble oxycodone or hydrocodone, with users unaware of the drug's presence. In early 2016, counterfeit pills of alprazolam containing fentanyl resulted in nine known death in Florida. As a result of these alarming changes in opioid synthesis, it is clear adolescents are more vulnerable to exposure to fentanyl or fentanyl analogs if they are abusing heroin or other prescription opioids. Reassuring trends include a decline in annual heroin abuse in the US among 12th graders since 2000, with a consistent 0.3% incidence in the past several years. Annual abuse of narcotics other than heroin in this same group has been declining since 2009 to approximately 4% in 2017.[2]

Carfentanil is an ultra-potent fentanyl analog that is used in veterinary medicine to anesthetize large animals. Carfentanil potency is approximately 100 times that of fentanyl. It was believed to be responsible for a large cluster of deaths in the Midwestern United States in the summer of 2017,[19] with continued sporadic reports of carfentanil recovered in law enforcement drug seizures.

Other fentanyl analogs include acetyl fentanyl, butyric fentanyl, furanyl fentanyl, and 4-methyl fentanyl. Despropynyl fentanyl was the most commonly identified fentanyl analog (other than fentanyl) in DEA drug seizures in 2017. Another synthetic opioid that has been commonly seized is U-47700, or 3,4-dichloro-N-[2-(dimethylamino) cyclohexyl]-N-methylbenzamide. U-47700, called "U-4" or "Pink" on the street, is approximately 7.5 times more potent than morphine. It became a Schedule I substance in 2016, and is believed to be responsible for at least 80 deaths in the US in 2017. Isopropyl-U-47700, 4 -methyl acetylfentanyl and N-methyl norfentanyl were all identified for the first time in DEA drug seizures in 2018.[3]

Synthetic opioids produce the expected toxidrome of miosis, respiratory depression, and central nervous system depression. Treatment is aimed primarily at reversing respiratory depression. Naloxone, as an opiate receptor antagonist, reverses the effects of synthetic opioids, but much higher doses may be necessary. Naloxone is safe and well tolerated, but any patient with an opioid dependence may be put into physiologic withdrawal. The general "starting" dose of naloxone would be 1 to 2 mg IV, with repeated doses every 2 to 3 minutes as necessary. A smaller dose of 0.4 mg IV can be used if the patient has spontaneous respirations and there is concern about opioid addiction and the potential for withdrawal. A maximum total dose of 10 mg of naloxone is recommended. If no effect is seen after 10 mg, consider an alternative diagnosis. Because the duration of naloxone is short (approximately 45 minutes), patients should be observed beyond the point of naloxone action. This practice is recommended in case the particular opioid abused has a longer duration of action compared to naloxone, with the significant risk of recurrent sedation and respiratory depression. Treatment may require the use of a naloxone drip, or definitive airway management with mechanical ventilation. Hypotension can be seen, but is generally mild and easily treated with intravenous fluid support.

VAPING

A recent development in adolescent health is the increasing use of electronic cigarettes (e-cigarettes) or other electronic vaping devices, as a delivery method for nicotine, marijuana, and other illicit drugs. The first successful commercial e-cigarette was available in 2003. Since then, use in middle school and high school students in the US has increased dramatically. In 2011, 0.6% of middle school students and 1.5% of high school students reported use of e-cigarettes. By 2015, this increased

to 5.4% and 16%, respectively. E-cigarettes are the most commonly used product in these adolescent groups,[20,21] with the perception of e-cigarettes as safer than traditional cigarettes.[22] However, a major concern with adolescent use of e-cigarettes is the increased risk of later traditional cigarette use and nicotine addiction, compared those who had never used the electronic version.[23,24]

Significant numbers of adolescents report that they have vaped cannabis in their lifetime.[25] When surveyed about which was the first substance vaped, teens reported use of nicotine mixed with flavors, as well as flavors-only substances, with the cannabis the third most common substance. Remember that any substance both heat-stable and solulizable can be used in an e-cigarette device. User testimonials on websites (reports that are anecdotal and unconfirmed) describe vaping synthetic cannabinoids, methamphetamine, cocaine, LSD, fentanyl, and dimethyltryptamine.[26] A survey of young adults in the United Kingdom suggests that a high percentage had vaped a recreational drug other than cannabis in their lifetime.[27]

One particular device that has received attention is branded as JUUL, with use of the device known colloquially as "juuling." JUUL devices resemble USB flash drives and are charged by plugging them into a computer or other USB charger. Initial marketing included youth-oriented imagery and themes, with JUUL now holding a majority of the current market share. It is possible the JUUL was purposely designed to mimic the appearance of devices readily found and used in schools. Internet searches on YouTube and Google showed that "stealth vaping," "hiding JUUL in school," and "JUUL at school" are popular searches.[28] Other brands have followed with similarly designed devices, including those that resemble pens, asthma inhalers, travel mugs, car keys, and remote controls.[28] In a group of 15- to 17-year-olds surveyed, 9.5% reported lifetime JUUL use and 6.1% reported current use of a JUUL device.[29] Because JUUL e-liquids pods contain nicotine, JUUL sale to minors is restricted in the United States. However, these products were easily available for internet purchase, including on eBay, until a Food and Drug Administration (FDA) action restricting sales occurred in April of 2018.[30] While teens are buying and using JUUL devices, only 25 to 37% of surveyed young adults were aware that JUUL always contains nicotine.[31]

CASE OUTCOME, DRUG SCREENS, AND POISON CENTERS

The 15-year-old patient was extubated within 24 hours and upon awakening, he stated he took something called "C4" or "CD4." PICU house staff documented internet searches of these terms and concluded that he took pramipexole, a dopamine agonist used to treat the symptoms of Parkinson's disease and restless legs syndrome. On review of the literature, a recent case report described a 19-year-old who inhaled "liquid acid" and presented with a generalized tonic clonic seizure, hyperthermia, tachycardia, hypertension, and acidosis. In the case report, liquid chromatography/mass spectroscopy showed that the patient was exposed to 2C-I (4-Iodo-2,5-dimethoxyphenethylamine).[32] With our patient stating he took "C4," it is most likely he abused a synthetic amphetamine in the 2C family and *not* pramixepole, a drug that does not explain all his signs and symptoms. After supportive critical care, our patient went on to a full recovery.

A standard toxicology mantra is "treat the patient, not the poison." In the acute care setting, identification of the ingested drug may not be possible, and will have little impact on initial emergency treatment decisions for patient stabilization. While direct antidotes exist for opioids and benzodiazepines, supportive care can be an effective treatment for both as well. Supportive measures, that ensure oxygenation, ventilation, perfusion, and glucose provision, are the standard of care for all the drugs of abuse described above.

The standard urine drug screen used by most US hospitals will not detect synthetic cannabinoids, synthetic cathinones and other synthetic amphetamines, fentanyl and fentanyl analogs, and most synthetic opioids. A number of studies have shown that drug screening rarely results in any change of management in both adult and pediatric patients being evaluated for drug ingestions.[33-36] In addition, urine drug screens can produce false positive results. Most important, a positive urine drug screen may not be indicative of toxicity or causality of symptoms. Therefore, the cessation of medical testing based on the results of urine drug screen may result in diagnostic error. "Comprehensive" drug screens, designed to detect legal pharmaceutical agents, will not detect the agents described above.

At this time, detection of synthetic compounds requires specific targeted recognition methods. University research laboratories, local coroner offices, and the regional poison center may be able to offer consulting and testing assistance if specific detection is needed. If the actual drug itself is present in the ED or still available on scene, obtaining the substance for laboratory analysis will produce the highest yield. With available substance for testing, law enforcement agencies, including the forensic laboratories of the local DEA office, may be

important partners in assisting case management. Laboratory determination of a substance, or a patient's urine or serum, may be pursued, but drug identification will likely require days. It may be of importance, from an investigative or clinical standpoint, to identify the specific substance sooner. To this end, historical identifiers, or nicknames for drugs, can be pursued. An Internet search of a slang term may help (or mislead, as in our case), but one useful and updated list of terms from the DEA can be found at https://ndews.umd.edu/sites/ndews.umd.edu/files/dea-drug-slang-terms-and-code-words-july2018.pdf. Other potentially useful websites include erowid.org, bluelight.org, drugs-forums.com, or reddit.com. Please note that most of the information on these sites contains unverified testimonials by individual users.

A critical source of expertise and clinical information contemporaneous to care of a poisoned or intoxicated patient is your regional poison center. The poison center should be contacted for all poisoned and intoxicated patients, particularly in the era of synthetically derived compounds. This allows regional toxicology experts to compile data and identify clusters of dangerous drug activity or exposure, not apparent to any single clinician treating a patient. The initial epidemic of bath salts cases in the US was signaled by a regional poison center.

There is also a high probability that any drug acquired on the street or the Internet either does not contain the desired drug, or contains one or more adulterants. For example, a large percentage of pills sold in the US as MDMA (or ecstasy) contains benzylpiperazine (BZP), a piperazine derivative and Schedule I substance that produces stimulatory and hallucinogenic effects. In addition, unusual adulterants have been found in the drug supply. In 2018, a number of cases of coagulopathy and at least one death resulted from adulteration of synthetic cannabinoids with a long-acting superwarfarin commonly found in rat poison.[37] In the late 2000s, much of the cocaine supply in the US was adulterated with levamisole, a drug with antihelminthic and immunomodulatory properties, used to treat cancer and inflammatory conditions. This adulterant caused significant neutropenia and purpuric rashes in cocaine users.[38,39] Quality control practices in the production and distribution of illegal drugs are deficient or nonexistent. Varying concentrations of any given drug can be found in different batches. This may result in exaggerated toxic effects if a patient uses the same volume, but higher concentration of drug. So too, if a certain volume produces a lack of desired effect due to low concentration, the user increases total intake to his or her detriment.[40]

With much to learn about new synthetically produced drugs and their adulterants, mimickers, antidotes, and treatments, the altered and poisoned teen can be a medical decision-making challenge. However, this critical information is immediately available by calling your regional poison center, with toxicology experts providing database information access, clinical expertise, and evidence-based management strategies.

SUMMARY

Adolescent drug abuse is a common problem. Novel substances and mechanisms of delivery have emerged over recent years. In addition, novel compounds continue to be found in the drug supply every year. The Internet and social media may facilitate the acquisition and abuse of these drugs by adolescents. Identification of these substances is generally not available in any clinically meaningful time frame. However, identification is generally not necessary for successful treatment of the patient. Contact with regional poison center experts provides clinical guidance contemporaneous to emergency care. Treatment of the majority of these intoxications is supportive.

DISCLOSURES

None

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