The Journal of Emergency Medicine, Vol. ■, No. ■, pp. 1–8, 2015

0736-4679/$ - see front matter

http://dx.doi.org/10.1016/j.jemermed.2014.12.038

Selected Topics: Toxicology

A COMMON SOURCE OUTBREAK OF SEVERE DELIRIUM ASSOCIATED WITH EXPOSURE TO THE NOVEL SYNTHETIC CANNABINOID ADB-PINACA

Michael D. Schwartz, MD,* Jordan Trecki, PHD,† Laura A. Edison, DVM, MPH,‡ Alaina R. Steck, MD,§ Justin K. Arnold, DO,§ and Roy R. Gerona, PHD‖

*Centers for Disease Control and Prevention, National Center for Environmental Health, Office of Environmental Health Emergencies, Atlanta, Georgia, †Drug Enforcement Administration, Office of Diversion Control, Drug and Chemical Evaluation Section, Springfield, Virginia, ‡Centers for Disease Control and Prevention, Epidemiology Program Office, Atlanta, Georgia, §Georgia Poison Center, Atlanta, Georgia, and ‖Department of Laboratory Medicine, University of California–San Francisco, San Francisco, California

Reprint Address: Michael D. Schwartz, MD, Centers for Disease Control, National Center for Environmental Health, Office of Environmental Health Emergencies, 1600 Clifton Road, MS F-09, Atlanta, GA 30333

☐ **Abstract—Background: Since 2009, synthetic cannabinoid (SC) use has emerged as a growing public health threat in the United States (US). Several outbreaks of unexpected, severe toxicity linked to SC use have been reported since 2012. Reports of varied and significant morbidity after SC use are expected to increase because newer compounds enter the marketplace more frequently as manufacturers attempt to circumvent regulatory efforts. Case Report: We report a cluster of 7 patients who experienced a spectrum of anxiety, delirium, psychosis, and aggressive behaviors after smoking the same SC-containing product at a party. An 8th patient with the same exposure source presented with delayed onset seizures. Biologic samples were analyzed for novel, newly identified SCs belonging to the FUBINACA family of compounds. A previously unknown SC, N-(1-amino-3, 3-dimethyl-1-oxobutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide (ADB-PINACA) was identified in biologic samples from 7 of the individuals. ADB-PINACA was identified in the SC-containing product ("Crazy Clown") seized by law enforcement and identified as the product smoked by the 8 patients in the reported cluster. Why Should an Emergency Physician Be Aware of This?: The information compiled using this cluster of cases, and a similar reported outbreak of altered mental status in Colorado, implicating the same SC (ADB-PINACA) and brands of SC-containing products, aided the US Drug Enforcement Administration in its temporary scheduling of ADB-PINACA and three other SCs. In this outbreak, close cooperation between public health and law enforcement allowed for a rapid intervention, which halted the outbreak by interrupting the common source and accelerated regulatory efforts to prevent further morbidity and mortality.** © **2015 Elsevier Inc.**

☐ **Keywords—synthetic cannabinoid; delirium; ADB-PINACA; cluster; outbreak; spice; K2; DEA scheduling**

INTRODUCTION

Synthetic cannabinoids (SCs) are a newly emerging public health threat. SCs ("Spice," "K2") collectively constitute >50 individual synthetic compounds that are part of this new designer drug epidemic. SCs typically are dissolved in a solvent, applied to dried plant material

Disclaimer for Drs. Schwartz and Edison: The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention or the Agency for Toxic Substances and Disease Registry.

Disclaimer for Dr. Trecki: The views expressed herein are those of the authors and do not necessarily represent the views of the Drug Enforcement Administration, the United States Department of Justice, or any officer or entity of the United States.

RECEIVED: 1 October 2014; FINAL SUBMISSION RECEIVED: 17 November 2014;
ACCEPTED: 21 December 2014

or herbal potpourri, and smoked as an alternative to marijuana. SC-containing products are marketed commercially as "herbal incense" and labeled "not for human consumption," both designations suggesting legitimacy. Users smoke SC-containing products expecting to evade standard urine drug screening and to experience a more intense psychoactive effect than with marijuana. The SCs tested so far are more potent than delta-9-tetrahydrocannabinol (THC), and reports of sympathomimetic effects and seizures from smoking SCs are more numerous than similar reported effects from smoking marijuana (1–3). Reports of cases and outbreaks of unpredicted, severe toxicity have increased as the number of SCs introduced to the market has risen. Seizures are one of the most common unpredictable toxicities reported after SC exposure (4–10). Chest pain and cardiovascular toxicity after SC use have also been reported (11,12). Two of the authors (MDS, RRG) have reported on a nationwide outbreak of acute kidney injury (AKI) associated with use of the novel SC XLR-11 (13). The recent outbreaks reported in Georgia and Colorado are the first involving clusters of cases with altered mental status and agitated delirium associated with a specific compound (14–16). Recently, the Arkansas K2 Consortium published a report of an isolated case of fatal psychosis after SC exposure (17).

CASE REPORT

Initial Epidemiological and Law Enforcement Investigation

On August 22, 2013, a hospital in Brunswick, Georgia called the Georgia Poison Center seeking management recommendations for 7 patients who presented simultaneously after smoking an SC-containing product at a party. The patients were not known to have any medical history, and all had been well previously on the day of presentation. On the evening of admission, all patients had been at the same party and smoked the same product. Glynn County (GA) police noted that this index cluster of 7 patients had been smoking a new shipment of "Crazy Clown," a synthetic incense made in Colorado and purchased from a smoke shop in Brunswick, GA. Emergency Medical Services (EMS) were called after 3 of the patients began behaving aggressively and transported all 7 patients to the emergency department (ED). The patients underwent laboratory evaluation with complete blood count, comprehensive metabolic panel, creatinine phosphokinase (CPK), coagulation profile, arterial or venous blood gas, and venous lactate.

Upon identifying the source of the implicated product smoked by the case patients, law enforcement personnel removed all Crazy Clown product from the smoke shop. Analysis of the product inventory by the Georgia Bureau of Investigation Crime Laboratory identified the novel pentyl indazole SC N-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide (ADB-PINACA) in samples of Crazy Clown (18).

Individual Case Descriptions

Case 1. Patient 1 was a 25-year-old male who was markedly agitated and combative upon EMS arrival. He required chemical sedation and intubation to control his extreme agitation. First documented vital signs were heart rate (HR), 130 beats per minute (bpm); blood pressure (BP), 142/56 mm Hg; respiratory rate (RR), 20 breaths per minute (mechanically ventilated); and oxygen saturation (SpO_2), 100%. His initial laboratory results were significant for an anion gap 15 mEq/L, venous lactate 3.13 mmol/L, and CPK 920 IU/L. All other results were within normal limits. He was admitted to the intensive care unit (ICU) and continued to have intermittent tachycardia and hypertension until hospital day (HD) 3, when he was extubated. Although he was initially confused after extubation, his mental status rapidly improved, and the hospital discharged him in his baseline state of health on HD 5.

Case 2. Patient 2 was a 24-year-old male who also was confused and agitated upon initial EMS evaluation. He required sedation and intubation for management of violent behavior. Initial vital signs were HR 132 bpm, BP 128/88 mm Hg, RR 22/min (mechanically ventilated), SpO_2 98%, and temperature, 98.9°F. His initial laboratory results were within normal limits, without acidosis or elevated CPK. Approximately 7 h after presentation, his vital signs had normalized. He was admitted only briefly to the ICU and was extubated 15 h after presentation. Once fully alert, this patient signed out against medical advice (AMA), declining further evaluation.

Case 3. Patient 3 was a 30-year-old male who was reported to be the most severely combative and aggressive of these 7 patients. EMS administered haloperidol and lorazepam and intubated him shortly thereafter. En route to the ED, he suffered a witnessed cardiac arrest and was resuscitated by paramedics. He had regained spontaneous circulation by the time he arrived in the ED. Vital signs upon arrival were HR 93 bpm, BP 118/69 mm Hg, RR 16/min (mechanically ventilated), SpO_2 99%, and temperature 98.9°F. Initial electrocardiogram (ECG) showed an anterior ST-elevation myocardial infarction, for which he was promptly transferred to the cardiac catheterization suite. Cardiac catheterization demonstrated complete occlusion of the left anterior descending, and the patient underwent successful balloon angioplasty. He was admitted

to the cardiac care unit and extubated uneventfully on HD 3. Once awake and alert, this patient reported that he had a medical history of familial hypercholesterolemia, as well as premature coronary artery disease and past cocaine use. He was discharged home on HD 5.

Case 4. Patient 4 was a 25-year-old female who was brought to the ED agitated, but alert and oriented. Her initial vital signs were HR 82 bpm, BP 117/61 mm Hg, RR 20/min, SpO_2 96% on room air (RA), and temperature 99.5°F. She left the hospital AMA after her initial blood draw. She did not receive any other interventions before she left the ED, and after her departure her laboratory results were reported to be within normal limits.

Case 5. Patient 5 was a 22-year-old female who was brought to the ED agitated, but alert and oriented. Her initial vital signs were HR 78 bpm, BP 105/63 mm Hg, RR 16/min, SpO_2 97% RA, and temperature 97.8°F. She elected to remain in the ED for initial evaluation and a period of observation. Her laboratory results and ECG were unremarkable, and she was discharged from the ED without requiring any therapeutic interventions.

Case 6. Patient 6 was a 21-year-old female who was brought to the ED alert and oriented, markedly anxious, but not aggressive. Initial vital signs were HR 112 bpm, BP 131/81 mm Hg, RR 14/min, SpO_2 96% RA, and temperature 98.0°F. She left the hospital AMA before a full evaluation was completed.

Case 7. Patient 7 was a 16-year-old female who was mildly agitated and anxious upon arrival to the ED, but was alert and oriented. Initial vital signs were HR 100 bpm, BP 153/71 mm Hg, RR 14/min, SpO_2 95% RA, and temperature 98.0°F. Her initial laboratory results and ECG were within normal limits. After receiving 1 L normal saline, her vital signs normalized and she was discharged from the ED in her baseline state of health.

Case 8. On September 3, 2013, the Georgia Poison Center received a call regarding a healthy 24-year-old male who presented with disorientation and delayed-onset seizures several days after smoking SCs sold under the brand names of Crazy Clown and "10X." He had purchased both substances from the same smoke shop in Brunswick, GA where the previously reported index cluster of 7 patients had obtained their product on August 22. One day after smoking 10X and Crazy Clown, the patient developed anorexia, nausea, and vomiting. Four days after smoking the products, the patient complained of difficulty concentrating and recalling short-term memory. Seven days after smoking the product, the patient had a generalized seizure for which he was evaluated in the ED, then rehydrated and released. The following day he appeared more disoriented and paranoid, according to his family.

Two days later, on September 3, he went to a different ED for evaluation; the poison center was consulted. His initial vital signs included an HR 85 bpm and BP 150/90 mm Hg. In the ED, he developed severe agitation, had a witnessed generalized seizure, and required intubation. Laboratory evaluation showed slight elevation of aspartate aminotransferase (AST) of 83 U/L and alanine aminotransferase (ALT) of 150 U/L, an elevated creatinine of 1.7 mg/dL, and elevated CPK of 500 U/L. His liver function tests peaked at AST 214 U/L and ALT 154 U/L. He had no further seizure activity and was extubated the following day. An electroencephalogram (EEG), magnetic resonance imaging (MRI) of the brain, and bedside neurologic examination were normal, and he was discharged home on HD 7 of this hospitalization. On the day of discharge, the patient had an episode of disorientation followed by an additional seizure that required readmission to the hospital. Repeat EEG and neurologic evaluation were again normal, and he was discharged the following day.

Case 9. On September 13, 2013, an emergency physician consulted the Georgia Poison Center about a 49-year-old, previously healthy, male Drug Enforcement Administration (DEA) agent who was exhibiting symptoms of SC intoxication. According to the agent, 2 days earlier, he and a partner were searching and manipulating packaged SC product during an unrelated seizure of drugs; the agent wore Latex gloves but no respiratory protection. The following morning, his wife observed that he was lethargic and forgetful. He complained of anxiety, difficulty sleeping, nausea and vomiting, and chest discomfort. His wife reported he was irritable and argumentative but not violent. Two days after exposure, he was evaluated at the ED and admitted overnight; his symptoms resolved with benzodiazepines and supportive care. Routine laboratory testing was normal, as were an MRI and a work-up for acute coronary syndrome. He consented to serial blood sampling for subsequent analysis for SCs.

Case Finding

To identify additional cases, the Georgia Department of Public Health (DPH) asked the Brunswick ED to report any other patients who reported use of SCs to the Coastal District (GA) Health Department for the period August 22 (index cluster of 7 patients) through September 9; Georgia DPH investigators then reviewed medical records of these patients.

Laboratory Analyses

At the time of presentation, the ED collected clinical samples from the 7 patients who were transported from the party in Brunswick on August 22. The poison center subsequently sent the samples to a reference laboratory for analysis to confirm SC exposure. The laboratory analyzed serum and plasma samples using liquid chromatography-quadrupole time-of-flight chromatography (LC-QTOF/MS, Agilent LC1260- QTOF/MS 6550; Agilent Technologies, Santa Clara, CA). A 250-μL aliquot of each sample was prepared for analysis by protein precipitation using 750 μL acetonitrile:methanol (95:5). A 2.5-μL aliquot of the resulting extract was injected into the LC-QTOF/MS for nontargeted MS scans. Compounds in each sample were separated using gradient elution chromatography in a C18 reverse-phase column (Agilent Poroshell, 2.1 $\times$ 100 mm, 3.0-μm particle size) at 50°C. Compounds eluting off the column were ionized by electrospray ionization in the positive and negative polarities in separate runs. Each MS analysis consists of two MS experiments: a TOF-MS experiment to detect all parent ions of compounds in each sample and an MS/MS scan to collect fragment ion data of parent ions exhibiting intensities > 5000 arbitrary units. The total ion chromatogram (TIC) obtained for each sample was then queried for the targeted analysis of 43 SCs and metabolites (retention times for these compounds are established through a validated method). No formula and retention time matches were found for any of these compounds. The TIC was then queried for formula matches using an expanded database of SCs and metabolites (115 compounds). Formula matches to ADB-PINACA or its N-pentanoic acid metabolite were detected in the samples. Confirmation and quantitation of both compounds were performed by isotope dilution method using reference standards that became available 6 weeks after potential matches to them were observed in the patients. Agilent MassHunter Qualitative and Quantitative Analysis analyzed data for each sample.

Process of DEA Emergency Scheduling

In addition to the Department for Health and Human Services (DHHS), DEA may temporarily schedule a substance under the following conditions: if it is not listed in any other schedule; if no exemption or approval is in effect for the drug; or if the Attorney General (or the delegated Deputy Administrator of the DEA) perceives an imminent threat to public safety. DEA is required to consider the following factors in its decision: the substance's history and current pattern of abuse; the scope, duration, and significance of abuse; and any risk to the public safety. DEA also considers available information regarding actual abuse, diversion from legitimate channels, and clandestine importation, manufacture, or distribution.

Before publishing a Final Order in the Federal Register, DEA is required to notify the Secretary of DHHS of the intention to temporarily place a substance into Schedule I of the Controlled Substances Act (CSA), as well as publish a Notice of Intent to temporarily schedule a substance. The Final Order may not be issued before the expiration of 30 days from the Notice of Intent to temporarily place a substance in Schedule I of the CSA. The Final Order temporarily scheduling a substance under the CSA is effective on the date of publication in the *Federal Register* and will remain in effect for a period of no less than 2 years, with a possible extension of 1 additional year.

RESULTS

Case Finding

DPH identified 22 patients who had been examined after using SCs during August 22–September 9, 2013. The patients were aged 16–57 years (median 25 years), and were predominantly male (18 [82%]). Patients experienced hyperglycemia (13 [59%]), hypokalemia (9 [41%]), acidosis (7 [32%]), tachycardia (13 [59%]), nausea/vomiting (8 [36%]), confusion/disorientation (7 [32%]), aggression (7 [32%]), somnolence/unresponsiveness (7 [32%]), and seizures (3 [14%]). Complications included pneumonia (2 patients), rhabdomyolysis (1 patient), and myocardial infarction (1 patient). Six (27%) patients were admitted to the ICU; 5 (23%) required assisted ventilation; none died (15).

Concentrations of ADB-PINACA and Metabolite in Biologic Samples

Table 1 shows the results of ADB-PINACA and ADB-PINACA-5-pentanoic acid metabolite found in the seven index cases from August 22 in Brunswick and from an unrelated secondary exposure in a DEA agent on September 11. No biospecimens were available from an 8th patient who presented with delayed-onset seizures on September 3 after smoking Crazy Clown and 10X. Noteworthy is the finding of a trace amount of ADB-PINACA metabolite in the first specimen obtained from the DEA agent 2 days after his occupational exposure.

Unlike most of the previous reports involving SC intoxication, admission blood samples from the Brunswick, GA cases were available for analysis. These blood samples obtained upon admission may have contributed to the higher levels detected in our patients, compared with those reported for other SC intoxications, when samples were collected at later times. In addition, the SC concentrations in products smoked by patients in this series

Table 1. Results of ADB-PINACA and n-Pentanoic Acid Metabolite in Biological Specimens

Patient	Sample Matrix	Date	Time	ADB-PINACA (ng/mL)	ADB-PINACA 5-Pentanoic Acid (ng/mL)
1	Serum	08/22	1958H	85	29
	Plasma	08/22	1958H	65	16
	Plasma	08/23	0530H	ND	57
	Plasma	08/24	0445H	ND	63
	Plasma	08/25	0730H	ND	76
2	Serum	08/22	2000H	307	32
		08/22	2000H	260	29
	Plasma	08/23	0600H	ND	109
		08/24	0611H	ND	52
	Plasma	08/25	0600H	ND	27
3	Plasma	08/22	2045H	61	28
	Serum	08/22	2045H	56	32
	Plasma	08/23	0455H	ND	55
4	Plasma	08/22	2030H	ND	24
5	Plasma	08/22	2033H	50	24
	Plasma	08/22	2033H	Insufficient sample volume	Insufficient sample volume
	Serum	08/22	2033H	50	22
	WB	08/22	2033H	ND	ND
6	Plasma	08/22	2100H	64	20
	Plasma	08/22	2100H	59	16
	Serum	08/22	2100H	133	22
	WB	08/22	2100H	ND	ND
	WB	08/22	2100H	ND	ND
7	Plasma	08/22	2105H	ND	23
8	NA			NA	NA
DEA	Serum	09/13	0221H	ND	12
	Serum	09/13	1224H	ND	ND
	Serum	09/13	1254H	ND	ND
	Serum	09/14	0251H	ND	ND
	Serum	09/15	0236H	ND	ND

ADB-PINACA = N-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-pentyl-1H-indazole-3-carboxamide; DEA = U.S. Drug Enforcement Administration agent; NA = not available; ND = not detected; WB = whole blood.

may have been higher than in other products, resulting in higher blood levels. Based on previous collaboration and work on the laboratory analysis of patient samples from SC intoxication cases, we knew the importance of securing admission samples for laboratory analysis to obtain measurable levels of SC in patient samples. As in previously reported cases of SC intoxication, in our cases, ADB-PINACA became undetectable in <12 h after patient admission. Animal studies and a few human studies on the SC JWH-018 have shown that aminoalkylindoles are rapidly metabolized (19). Later studies and case reports with reported levels of other aminoalkylindoles, including JWH-073, JWH-081, JWH-250, AM-2201, and XLR-11, support this observation (20–22). Hydroxylation of the alkyl chain attached to the indole moiety and its subsequent oxidation to a carboxylic acid derivative are two of the major metabolic reactions undergone by aminoalkylindoles (19,23). ADB-PINACA undergoes similar metabolic transformations; its N-pentanoic acid metabolite was detected in all patient samples, and unlike the parent compound, the metabolite is detectable in serum or plasma samples for much longer. In a number of samples obtained from the same time, some differences were observed in the measured levels of ADB-PINACA or its metabolite. Variation in extraction efficiency can explain these differences. Because serum is cleaner than plasma, our laboratory achieves better recoveries in serum. Differences in sampling and sample processing may have also contributed to the observed differences.

Emergency Scheduling and Enforcement

In the state of Georgia, the ADB-PINACA compound is categorized as a Schedule I substance by Official Code of Georgia Annotated 16-30-31, as part of Chase's Law, which was passed by the Georgia General Assembly in the 2012 session (18). The smoke shop owner was charged on August 26, 2013 with distribution of a Schedule 1 controlled substance under Georgia law. The Brunswick ED has reported no additional patients who used SCs. The information collected from both this outbreak and the similar outbreak in Colorado was included in the DEA's Emergency Scheduling order effective February 10, 2014 (79 FR 7577).

WHY SHOULD AN EMERGENCY PHYSICIAN BE AWARE OF THIS?

The ongoing epidemic of designer drug abuse is entering its 5th year in the United States (US). Already, the particular SC compounds present in SC-containing products prevalent in the US market have changed several times since the introduction of SC-containing products in 2009. These changes in manufacture of SC compounds occur in response to efforts at regulation and enforcement, rather than concerns about user safety. As a result, the potential that any one SC compound will result in a severe, unpredictable organ-specific or systemic toxicity is greatly increased. At the same time, detecting these compounds with laboratory analysis and thus linking confirmed exposures with adverse health effects is challenging, because newer compounds are developed and marketed so rapidly.

The large number of designer drugs currently on the market, and the lack of readily available confirmatory laboratory testing, makes identifying the exact etiology in any particular clinical case challenging. Sophisticated laboratory capabilities are not available in most hospitals, and lack of analytical standards may make confirmatory testing on clinical specimens difficult. Even if confirmatory laboratory testing were immediately available, the results would not likely alter management. SC compounds do not give a positive result for marijuana on urine

immunoassay drug screens. Absent a history of Spice or "synthetic marijuana" use by the patient, a clue to SC intoxication might be the report of using marijuana with a negative urine drug screen. Severe signs, such as seizures, sympathomimetic toxidrome, or organ-specific toxicity, such as AKI, in the context of reported marijuana use, might also suggest use of an SC-containing product.

There are a number of ways to report SC intoxication cases. Clusters of adverse health effects potentially related to SC product use can be reported either to the local poison center or to local public health departments. Cases of severe SC intoxication, unusual toxicity, death, or multiple presentations for SC intoxication clustered in time and space are important public health events; rapid identification of these events will allow public health officials to better support local practitioners.

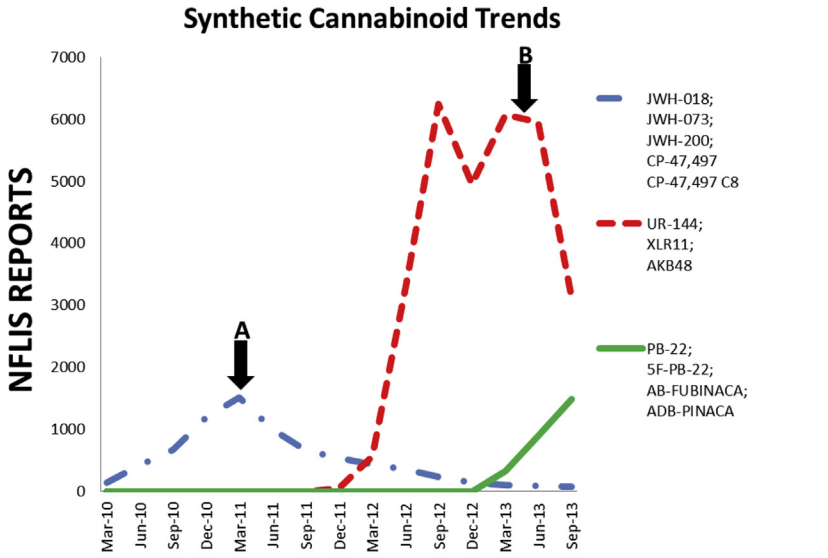
SCs are synthetic compounds that activate cannabinoid receptors CB1 and CB2 and are functionally similar to delta-9-THC found in cannabis. A small number of SCs were originally designed as research chemicals to investigate the function of the endocannabinoid receptor systems in the body. They have no legitimate medical purpose. Despite their labeling by users and the media as "synthetic marijuana" or a "legal high," SC-containing products are neither. Users smoke SC-containing products expecting the same psychotropic effects as from smoking marijuana. The compounds themselves are primarily synthesized by foreign chemists and without quality controls or manufacturing standards. The compounds are smuggled into the United States and, again without quality control or safeguards against contamination, dissolved in solvent and applied to dried botanical mixtures. The uniformity of SC distribution in a particular packet of product can vary greatly, as can mixtures of various SCs in a single product. The SC-containing product is marketed in colorful and equally colorfully named packages, marked "not for human consumption" and sold in smoke shops and gas stations to a younger, often first-time drug-using, demographic.

In November 2008, US authorities first intercepted an SC-containing product entering the United States. Since that time, drug trend reports from the Substance Abuse and Mental Health Services Administration, surveys of high school students, calls to state poison centers after SC exposure, and visits to EDs for adverse health effects after use are all evidence of the rapid growth of the SC epidemic in just 5 years. The outbreak reported here is yet another example of the types of expected public health consequences as the SC epidemic progresses. The first generations of SC-containing products, although abused recreationally, contained compounds that were previously developed for research purposes; therefore, some pharmacokinetic and biologic activity data were available. However, subsequent generations of SCs are novel compounds for which no pharmacologic or chemical information is available. For example, ADB-PINACA did not appear in the scientific literature before its emergence in the designer drug market; the Brunswick, GA, outbreak was, therefore, toxicologists' and law enforcement's first encounter with the drug. Therefore, as novel SCs appear on the designer drug scene, novel toxicities are expected to follow. Our group first reported a nationwide outbreak of AKI associated with use of a then-newly emerged compound, XLR-11, in 2012 (13). Additional reports of AKI associated with XLR-11 use followed in Alabama and in Oregon (24,25).

The outbreak associated with ADB-PINACA in Georgia was followed a week later by reports in Colorado of significant increases in hospitalization for altered mental status after using SC-containing products, two brands of which—Crazy Clown and 10X—were encountered in Brunswick (14,16). Testing of SC products in Colorado ("Black Mamba," Crazy Clown, and 10X) has identified the presence of ADB-PINACA and the related AD-BICA (N-(1-amino-3,3-dimethyl-1-oxobutan-2-yl)-1-pentyl-1H-indole-3-carboxamide). No testing of clinical samples from the Colorado outbreak has been reported.

Joint Public Health and Law Enforcement Efforts

Two trends inform the increase in severe, unpredicted, and otherwise idiosyncratic toxicities associated with SC use such as the one reported here: 1) heightened efforts at regulation of SC-containing products, followed by 2) the rapid introduction of newer SC compounds into the marketplace in an effort to circumvent regulations. Figure 1 shows how regulatory efforts are successful in leading to a rapid decline in the newly scheduled cannabinoids, while also heralding the appearance of entirely new groups of compounds in the marketplace. The speed with which new SCs are introduced precludes efforts to systematically research and demonstrate toxicity through traditional methods. By the time toxicokinetic studies or absorption, distribution, metabolism, and excretion data are available, and before longitudinal animal assays can be completed, the relevant compounds will already be replaced on the designer drug market. At the time of the outbreak reported here, analytical standards were unavailable, and it was 6 weeks before the ADB-PINACA findings we report could be quantitated. Obtaining standards of the theoretical metabolites of ADB-PINACA caused an additional delay. Faced with the challenge of previously unknown SC compounds, the DEA may use clinical reports of adverse health effects and outbreak reports of severe or previously undescribed toxicities to assist and inform their regulatory efforts.



A - March 1, 2011 - Temporary placement of JWH-018, JWH-073 JWH-200, CP-47,497 and CP-47,497 C8 into Schedule I of the CSA (76 FR 11075)

B - May 16, 2013 - Temporary placement of UR-144, XLR11 and AKB48 into Schedule I of the CSA (78 FR 28735)

* Data obtained from supplemental material for DEA's Final Order for Temporary Placement of Four Synthetic Cannabinoids Into Schedule I (79 FR 7577, February 10, 2014)

† 2013 Q3 and Q4 NFLIS Data not complete

NFLIS – National Forensic Laboratory Information System

Figure 1. Synthetic cannabinoid marketplace trends and regulatory actions*,†. CSA = Controlled Substances Act; DEA = Drug Enforcement Agency.

After the introduction of SC-containing products to the US marketplace in 2009, the predominantly circulating SC compounds were former research chemicals, such as aminoalkylindoles (JWH compounds developed by John W. Huffman at Clemson University in the 1990s) and cyclohexylphenols (CP compounds developed and patented by Pfizer). The first DEA scheduling of five SCs (JWH-018; -073; -20; CP 47,497; and 47,498c8) occurred in March 2011. Subsequently, in the face of a growing epidemic of SC misuse and abuse, the Synthetic Drug Abuse Prevention Act signed on July 9, 2012 listed 15 SCs as well as a number of other designer drugs, including two synthetic cathinones (also known as "bath salts") and nine phenylethylamine hallucinogens.

In early 2012, the National Forensic Laboratory Information System (NFLIS) reported a new generation of SC compounds, the tetramethylcyclopropyl ketone indoles and indazoles, UR-144, XLR-11 (5F-UR-144), and AKB-48, which were detected in SC-containing products analyzed by state, local, and federal laboratories. NFLIS-combined seizure data for all three compounds demonstrated 5643 positive findings for these SCs in the third quarter of 2012 (26). Thus, our previous investigation of an outbreak of AKI associated with XLR-11 occurred when XLR-11 was the predominantly circulating SC in the market. In May 2013, the DEA temporarily scheduled UR-144, XLR-11 (5F-UR-144), and AKB-48. Within the various components of the scheduling action, DEA cited the nationwide reports of AKI associated with XLR-11 as evidence of a public health threat, demonstrating the value public health investigations may bring to regulatory and enforcement efforts during this rapidly evolving SC epidemic.

The information compiled during the investigation of the Brunswick outbreak, and the similar outbreak of delirium associated with the same compound reported in Colorado, aided the DEA in its temporary scheduling of ADB-PINACA and three other SCs on February 10, 2014 (79 FR 7577).

REFERENCES

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

toxicology of synthetic cannabinoids. Prog Neuropsychopharmacol Biol Psychiatry 2012;39:234–43.
2. Forrester MB, Kleinschmidt K, Schwarz E, Young A. Synthetic cannabinoid and marijuana exposures reported to poison centers. Hum Exp Toxicol 2012;31:1006–11.
3. Hoyte CO, Jacob J, Monte AA, Al-Jumaan M, Bronstein AC, Heard KJ. A characterization of synthetic cannabinoid exposures reported to the National Poison Data System in 2010. Ann Emerg Med 2012;60:435–8.
4. Simmons J, Cookman L, Kang C, Skinner C. Three cases of "spice" exposure. Clin Toxicol (Phila) 2011;49:431–3.
5. Lapoint J, James LP, Moran CL, Nelson LS, Hoffman RS, Moran JH. Severe toxicity following synthetic cannabinoid ingestion. Clin Toxicol (Phila) 2011;49:760–4.
6. Schneir AB, Baumbacher T. Convulsions associated with the use of a synthetic cannabinoid product. J Med Toxicol 2012;8:62–4.
7. Harris CR, Brown A. Synthetic cannabinoid intoxication: a case series and review. J Emerg Med 2013;44:360–6.
8. Tofighi B, Lee JD. Internet highs—seizures after consumption of synthetic cannabinoids purchased online. J Addict Med 2012;6:240–1.
9. Pant S, Deshmukh A, Dholaria B, et al. Spicy seizure. Am J Med Sci 2012;344:67–8.
10. McQuade D, Hudson S, Dargan PI, Wood DM. First European case of convulsions related to analytically confirmed use of the synthetic cannabinoid receptor agonist AM-2201. Eur J Clin Pharmacol 2013;69:373–6.
11. Mir A, Obafemi A, Young A, Kane C. Myocardial infarction associated with use of the synthetic cannabinoid K2. Pediatrics 2011; 128:e1622–7.
12. Young AC, Schwarz E, Medina G, et al. Cardiotoxicity associated with the synthetic cannabinoid, K9, with laboratory confirmation. Am J Emerg Med 2012;30:1320.
13. Centers for Disease Control and Prevention (CDC). Acute kidney injury associated with synthetic cannabinoid use—multiple states, 2012. MMWR Morb Mortal Wkly Rep 2013;62:93–8.
14. Monte AA, Bronstein AC, Cao DJ, et al. An outbreak of exposure to a novel synthetic cannabinoid. N Engl J Med 2014;370:389–90.
15. Centers for Disease Control and Prevention (CDC). Notes from the field: Severe illness associated with synthetic cannabinoid use—Brunswick, Georgia, 2013. MMWR Morb Mortal Wkly Rep 2013;62:939.
16. Centers for Disease Control and Prevention (CDC). Notes from the field: severe illness associated with reported use of synthetic marijuana—Colorado, August-September 2013. MMWR Morb Mortal Wkly Rep 2013;62:1016–7.
17. Patton AL, Chimalakonda KC, Moran CL, et al. K2 toxicity: fatal case of psychiatric complications following AM2201 exposure. J Forensic Sci 2013;58:1676–80.
18. Georgia Bureau of Investigation. Herbal Incense Seized in Glynn County Determined to be Schedule I Substance. Available at: http://gbi.georgia.gov/press-releases/2013-09-12/herbal-incense-seized-glynn-county-determined-be-schedule-i-substance. Accessed January 28, 2014.
19. Wintermeyer A, Möller I, Thevis M, et al. In vitro phase I metabolism of the synthetic cannabimimetic JWH-018. Anal Bioanal Chem 2010;398:2141–53.
20. Kacinko SL, Xu A, Homan JW, McMullin MM, Warrington DM, Logan BK. Development and validation of a liquid chromatography-tandem mass spectrometry method for the identification and quantification of JWH-018, JWH-073, JWH-019, and JWH-250 in human whole blood. J Anal Toxicol 2011;35:386–93.
21. Dresen S, Kneisel S, Weinmann W, Zimmermann R, Auwarter V. Development and validation of a liquid chromatography-tandem mass spectrometry method for the quantitation of synthetic cannabinoids of the aminoalkylindole type and methanandamide in serum and its application to forensic samples. J Mass Spectrom 2011;46: 163–71.
22. M1 Hutter, Moosmann B, Kneisel S, Auwärter V. Characteristics of the designer drug and synthetic cannabinoid receptor agonist AM-2201 regarding its chemistry and metabolism. J Mass Spectrom 2013;48:885–94.
23. Hutter M, Broecker S, Kneisel S, Auwärter V. Identification of the major urinary metabolites in man of seven synthetic cannabinoids of the aminoalkylindole type present as adulterants in 'herbal mixtures' using LC-MS/MS techniques. J Mass Spectrom 2012;47: 54–65.
24. Bhanushali GK, Jain G, Fatima H, Leisch LJ, Thornley-Brown D. AKI associated with synthetic cannabinoids: a case series. Clin J Am Soc Nephrol 2013;8:523–6.
25. Buser GL. Acute kidney injury associated with synthetic cannabinoid use—Oregon, 2012. Abstract presented at the 62nd Annual Epidemiologic Intelligence Service Conference, April 25, 2013, Atlanta, GA.
26. Drug Enforcement Administration (DEA). Schedules of Controlled Substances: Temporary Placement of Three Synthetic Cannabinoids Into Schedule I. May 16, 2013. (78 FR 28735).