ORIGINAL ARTICLE

"Zombie" Outbreak Caused by the Synthetic Cannabinoid AMB-FUBINACA in New York

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ABSTRACT

BACKGROUND

New psychoactive substances constitute a growing and dynamic class of abused drugs in the United States. On July 12, 2016, a synthetic cannabinoid caused mass intoxication of 33 persons in one New York City neighborhood, in an event described in the popular press as a "zombie" outbreak because of the appearance of the intoxicated persons.

METHODS

We obtained and tested serum, whole blood, and urine samples from 8 patients among the 18 who were transported to local hospitals; we also tested a sample of the herbal "incense" product "AK-47 24 Karat Gold," which was implicated in the outbreak. Samples were analyzed by means of liquid chromatography–quadrupole time-of-flight mass spectrometry.

RESULTS

The synthetic cannabinoid methyl 2-(1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamido)-3-methylbutanoate (AMB-FUBINACA, also known as MMB-FUBINACA or FUB-AMB) was identified in AK-47 24 Karat Gold at a mean (±SD) concentration of 16.0±3.9 mg per gram. The de-esterified acid metabolite was found in the serum or whole blood of all eight patients, with concentrations ranging from 77 to 636 ng per milliliter.

CONCLUSIONS

The potency of the synthetic cannabinoid identified in these analyses is consistent with strong depressant effects that account for the "zombielike" behavior reported in this mass intoxication. AMB-FUBINACA is an example of the emerging class of "ultrapotent" synthetic cannabinoids and poses a public health concern. Collaboration among clinical laboratory staff, health professionals, and law enforcement agencies facilitated the timely identification of the compound and allowed health authorities to take appropriate action.

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Commonly abused drugs are undergoing a period of proliferation and diversification, with a corresponding increase in the challenges faced by emergency and critical care physicians, substance abuse professionals, psychiatrists, and toxicologists. New psychoactive substances provide users with alternatives to older and better-characterized drugs of abuse, such as amphetamines, heroin, cocaine, and cannabis. Of the more than 540 new psychoactive substances that have been reported to the United Nations Office on Drugs and Crime,[1] synthetic cannabinoids are the fastest growing class, with more than 177 identified by the agency in 2014 and 24 new synthetic cannabinoids reported by Europol in 2015.[1-3] Initially developed by academic chemists and pharmaceutical scientists in the United States and Europe as ligands for studying the endocannabinoid system, synthetic cannabinoids share no structural commonality with the plant cannabinoid Δ^9-tetrahydrocannabinol (Δ^9-THC) found in cannabis[4] (Fig. 1). Synthetic cannabinoids shifted from research tools to drugs of abuse in 2008, when herbal mixtures known as the brands "Spice" (in Europe) and "K2" (in North America) were found to contain JWH-018 and CP 47,497-C8.[9] Since then, new synthetic cannabinoids have been developed in clandestine laboratories in China and South Asia and distributed by "darknet" retailers (e.g., Silk Road, Silk Road 2.0, and Pandora), street drug dealers, and organized-crime groups as inexpensive alternatives to traditional drugs of abuse.[10-13] Figure 1 provides a summary of the structural changes that have been found in these drugs since surveillance started in 2009.

Typically, synthetic cannabinoids are dissolved in solvent, applied to an inert herbal substrate, and smoked in a fashion similar to cannabis.[13] In the past 8 years, synthetic cannabinoids have been associated with serious adverse effects. The undesirable effects most commonly reported by users include drowsiness, lightheadedness, and fast or irregular heartbeat.[13-15] More severe clinical features, including psychosis, delirium, cardiotoxicity, seizures, acute kidney injury, hyperthermia, and death, have also been noted.[16-18] Depression of the central nervous system (CNS) is consistent with the potent cannabinoid receptor 1 agonist activity that has been reported for many synthetic cannabinoids, cardiotoxicity may be due to inhibition of the alpha subunit of potassium channels in cardiomyocytes, and autonomic symptoms may be due to the affinity of some cannabinoids for serotonin 2B receptors.[19] Some synthetic cannabinoids also possess agonist activity at dopamine receptors in vitro,[19] and substantial changes in dopamine signaling have been observed in a cannabinoid user in the midst of a severe withdrawal syndrome.[20]

The synthetic cannabinoid AB-FUBINACA (Fig. 1) was developed by Pfizer and described in a patent in 2009.[21] AB-FUBINACA was first identified in synthetic cannabinoid products in Japan in 2012[22] and was designated as a Schedule I controlled substance in the United States in January 2014.[23] On July 3, 2014, an ester analogue of AB-FUBINACA, methyl 2-(1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamido)-3-methylbutanoate (AMB-FUBINACA), was discovered in a product called "Train Wreck 2" in Louisiana and was immediately prohibited through emergency rule by the State of Louisiana.[24] More recently, AMB-FUBINACA appeared in a product found in New York City that resulted in the hospitalization of multiple persons on the morning of July 12, 2016, and turned a block in the Bedford–Stuyvesant area of Brooklyn into what was described by the lay press as a "zombieland."[25,26]

Description of Index Patient

On July 12, 2016, the New York City Emergency Medical Services (EMS) was dispatched to the scene of a multiple-casualty incident in the borough of Brooklyn in New York City. First responders reported that there were multiple persons at the scene, all of whom had a degree of altered mental status that was described by bystanders as "zombielike." Subsequent media reports of the outbreak on July 12, 2016, identified 33 persons exposed to an unknown drug, of whom 18 (number confirmed by law enforcement) were transported to two local medical centers. The ages of the persons requiring transport were 25 to 59 years (mean, 36.8 years), and all the persons were male. Eight of the persons identified themselves to emergency medical staff as homeless.

The clinical features in this outbreak were typified by the index patient, a man who was 28 years of age and who was described by EMS providers at the scene as being slow to respond to questioning and as having a "blank stare." Prehospitalization interventions included the administration of supplemental oxygen and cardiac

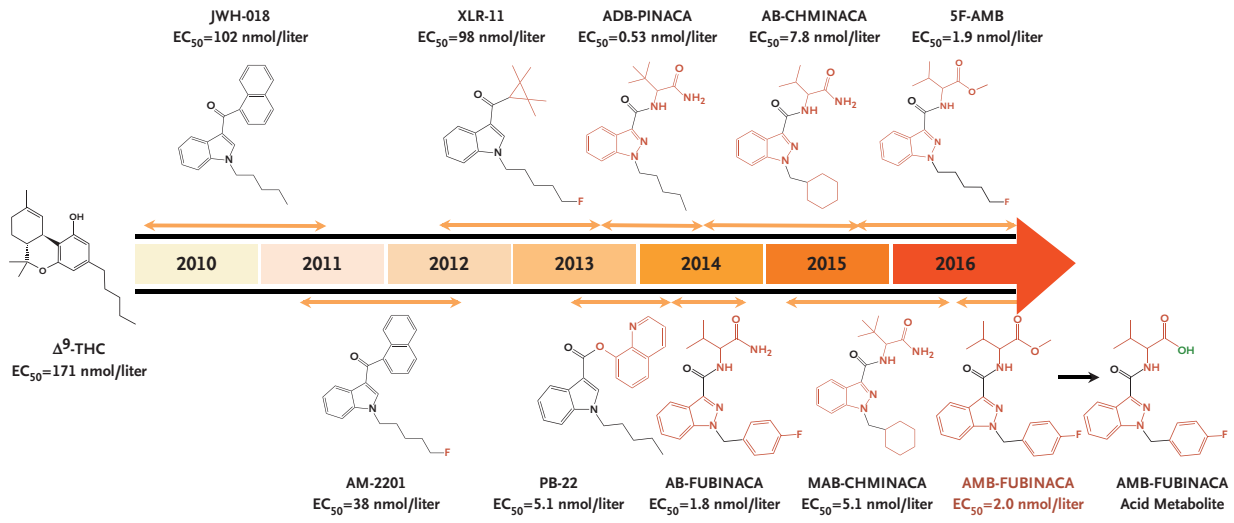


Figure 1. Evolution of Synthetic Cannabinoid Structures.

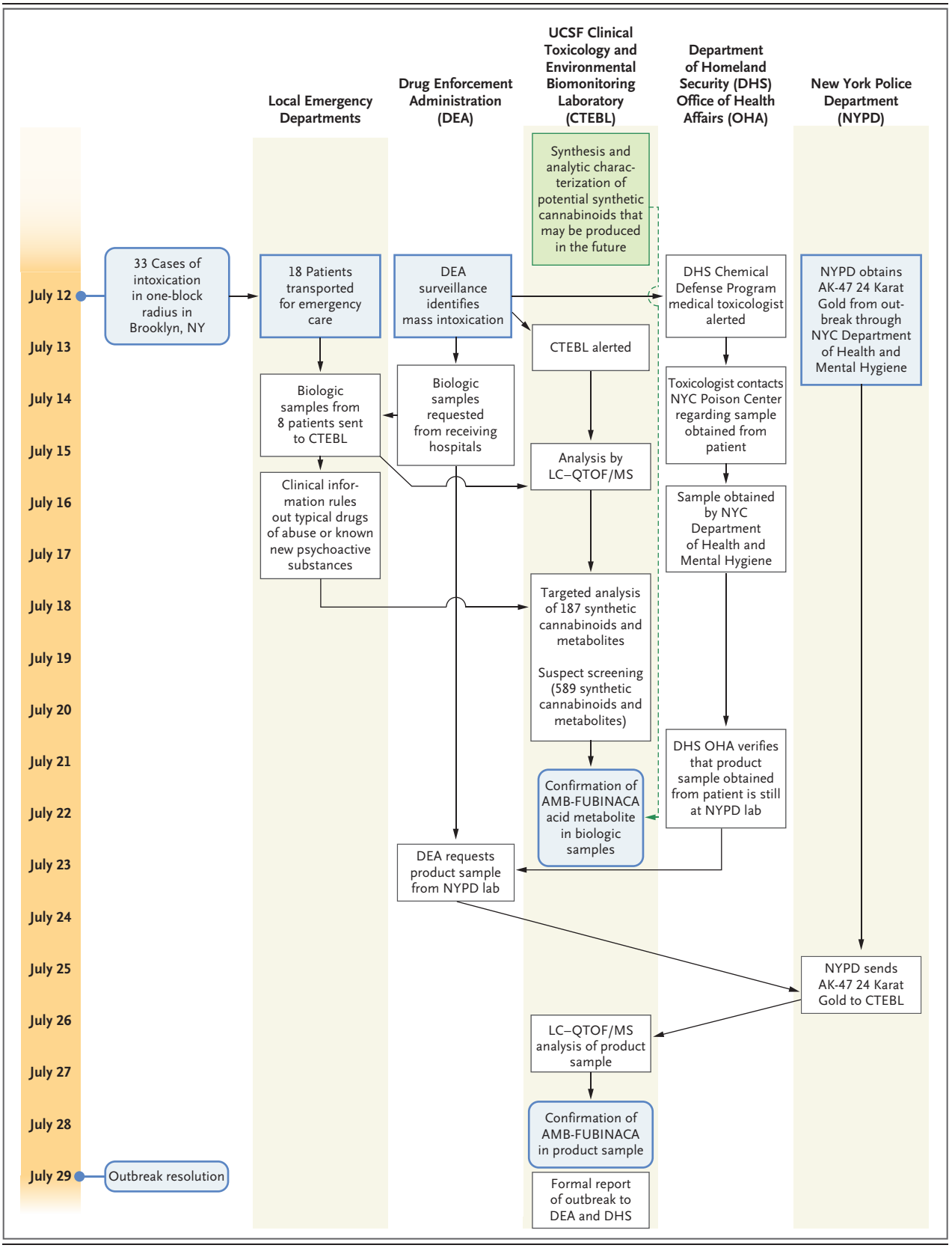
For each cannabinoid, the in vitro effective concentration required for 50% maximal response (EC_{50}) and the molecular structure are shown. The structure of the acid metabolite of methyl 2-(1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamido)-3-methylbutanoate (AMB-FUBINACA) is also shown. Double-sided orange arrows indicate the periods during which these cannabinoids were observed by the University of California, San Francisco, Clinical Toxicology and Environmental Biomonitoring Laboratory in the course of synthetic cannabinoid surveillance. Red structural moieties in the molecular structures indicate new structural motifs within the synthetic cannabinoids. The AMB-FUBINACA acid metabolite is shown with the site of ester hydrolysis highlighted in green. Note that the EC_{50} values provided are from in vitro fluorometric assays of membrane potential in cells transfected with the human cannabinoid receptor 1[5-8] and do not necessarily correspond to the potency of these agents in humans. Δ^9-THC denotes Δ^9-tetrahydrocannabinol.

monitoring. In the emergency department, the patient was lethargic but arousable to tactile stimuli. His heart rate was 88 beats per minute, blood pressure 101/61 mm Hg, respiratory rate 21 breaths per minute, body temperature 36.7°C (98°F) orally, and oxygen saturation 95% while he was breathing ambient air. Physical examination revealed no evidence of trauma. The pupils in both eyes were 4 mm and reactive; there was no facial asymmetry or excessive salivation noted. The patient was sweating. His lungs were clear to auscultation, and his heart sounds were normal. His bowel sounds were normoactive, and a skin examination revealed no evidence of excessive sweating, flushing, or lesions. The patient had no focal neurologic findings and no hyperreflexia or increased muscle tone. His overall score on the Glasgow Coma Scale was 13 (scores range from 3 to 15, with 15 being normal); his scores for eye response and for verbal response were 4, and his score for motor response was 5. He had intermittent periods of "zombielike" groaning and slow mechanical movements of the arms and legs.

Laboratory analysis, including a complete blood count, a comprehensive metabolic panel, urinalysis, and a urine immunoassay screening test for amphetamines, cocaine, phencyclidine, opiates, methadone, THC, barbiturates, benzodiazepines, tricyclic antidepressants, and serum ethanol level revealed no abnormalities. An electrocardiogram showed a normal sinus rhythm without evidence of acute myocardial injury or conduction abnormalities. Normal results of routine laboratory testing were found in the other seven patients who were treated at the same hospital.

The patient was placed in the observation unit; his lethargy resolved and his behavior normalized approximately 9 hours after his arrival. He offered no further clarifying history other than to confirm a first-time inhalational exposure to the substance contained in a packet, and he was discharged.

A description of the collaborative work among clinicians and various agencies that was undertaken from the time of the outbreak until the causative agent was identified is summarized in Figure 2. The Drug Enforcement Administration (DEA) and the Office of Health Affairs of the


Local Emergency Departments
Drug Enforcement Administration (DEA)
UCSF Clinical Toxicology and Environmental Biomonitoring Laboratory (CTEBL)
Department of Homeland Security (DHS) Office of Health Affairs (OHA)
New York Police Department (NYPD)
July 12
July 13
July 14
July 15
July 16
July 17
July 18
July 19
July 20
July 21
July 22
July 23
July 24
July 25
July 26
July 27
July 28
July 29
33 Cases of intoxication in one-block radius in Brooklyn, NY
18 Patients transported for emergency care
DEA surveillance identifies mass intoxication
Synthesis and analytic characterization of potential synthetic cannabinoids that may be produced in the future
DHS Chemical Defense Program medical toxicologist alerted
NYPD obtains AK-47 24 Karat Gold from outbreak through NYC Department of Health and Mental Hygiene
CTEBL alerted
Biologic samples from 8 patients sent to CTEBL
Biologic samples requested from receiving hospitals
Toxicologist contacts NYC Poison Center regarding sample obtained from patient
Analysis by LC–QTOF/MS
Clinical information rules out typical drugs of abuse or known new psychoactive substances
Sample obtained by NYC Department of Health and Mental Hygiene
Targeted analysis of 187 synthetic cannabinoids and metabolites
Suspect screening (589 synthetic cannabinoids and metabolites)
DHS OHA verifies that product sample obtained from patient is still at NYPD lab
Confirmation of AMB-FUBINACA acid metabolite in biologic samples
DEA requests product sample from NYPD lab
NYPD sends AK-47 24 Karat Gold to CTEBL
LC–QTOF/MS analysis of product sample
Confirmation of AMB-FUBINACA in product sample
Formal report of outbreak to DEA and DHS
Outbreak resolution

Department of Homeland Security became aware of this outbreak because of its scale and rapid evolution and because of the media coverage. On the basis of the fact that this was a large local outbreak and that the mode of drug exposure was smoking, it seemed possible that a potent synthetic cannabinoid agonist was involved, but patient interviews provided no indication of the identity of the compound. The DEA subsequently obtained biologic samples from 8 of the 18 patients in the outbreak who were transported for medical care, including the patient described above, and sent the samples to their collaborators for comprehensive drug analysis with the use of high-resolution mass spectrometry. In addition, a sample of the product that had been smoked by another patient who was brought to the emergency department and that had been turned over to the New York City Department of Health and Mental Hygiene and given to the New York Police Department Crime Laboratory was also analyzed. The implicated product — "AK-47 24 Karat Gold," shown in Figure 3 — consisted of agglutinated herbal material that had been divided into aliquots in eight small blue bags.

METHODS

Several aliquots of the product (AK-47 24 Karat Gold) and blood and urine samples from eight patients were sent to the Clinical Toxicology and Environmental Biomonitoring Laboratory at the University of California, San Francisco. Samples were analyzed by means of liquid chromatography–quadrupole time-of-flight mass spectrometry (LC–QTOF/MS) (Agilent LC 1260-QTOF/MS 6550). Quantitative analysis of each confirmed drug or metabolite was performed with the use of the isotope dilution method with a 10-point calibration curve. Further details of the toxicologic analyses are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Figure 2 (facing page). Timeline and Workflow of Collaboration Leading to the Resolution of the Outbreak.
LC–QTOF/MS denotes liquid chromatography–quadrupole time-of-flight mass spectrometry, NYC New York City, and UCSF University of California, San Francisco.

Figure 3. AK-47 24 Karat Gold Foil Wrapper Containing Herbal Products Recovered from a Patient Involved in the Outbreak.
Also shown are three of the eight small blue bags containing aliquots of the agglutinated herbal material.

RESULTS

ANALYSIS OF THE MATERIAL RECOVERED BY THE POLICE

LC–QTOF/MS analysis of the herbal product revealed a unique signal at a concentration of 1 mg per milliliter, which corresponded to AMB-FUBINACA. The signal was cross-referenced and confirmed by comparison with an analytic standard and the published literature.[27] The concentration of AMB-FUBINACA in several samples from the product ranged from 14.2 to 25.2 mg per gram, with a mean (±SD) concentration of 16.0±3.9 mg per gram (Table 1). AMB-FUBINACA was confirmed in a swab taken from the interior of the foil wrapper.

ANALYSIS OF BLOOD AND URINE FROM THE PATIENTS

No AMB-FUBINACA parent compound was detected in the blood or urine of the patients, but its de-esterified acid metabolite, 2-(1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamido)-3-methylbutanoic acid, was detected in every patient, with serum concentrations ranging from 77 to 636 ng per milliliter (or ppb) (Table 2). The urine concentration of the acid metabolite of AMB-FUBINACA was 165 ng per milliliter in the sample from Patient C and was below the limit of detection in the sample from Patient E. No other illicit drugs were observed in samples obtained from the patients. In one set of serial serum samples (from

Table 1. Concentrations of AMB-FUBINACA in Eight Individually Wrapped Aliquots of Botanical Material Obtained from AK-47 24 Karat Gold.*

Aliquot	AMB-FUBINACA Concentration
	mg/g
1	14.5
2	16.1
3	14.5
4	15.2
5	14.2
6	12.5
7	25.2
8	16.1
Mean (±SD) for all aliquots	16.0±3.9

* AMB-FUBINACA denotes methyl 2-(1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamido)-3-methylbutanoate.

Patient C), clearance of the drug was observed as the serum concentration decreased from 245 to 155 ng per milliliter over a period of 14 hours.

DISCUSSION

AMB-FUBINACA is a potent indazole synthetic cannabinoid that reflects the continued evolution of chemical structures of cannabinoid receptor agonists (Fig. 1). Recent in vitro pharmacologic studies of the actions of AMB-FUBINACA at the cannabinoid receptor 1 indicate that it is 85 times as potent as Δ^9-THC and 50 times as potent as JWH-018, which was found in the early outbreaks of "K2" synthetic cannabinoid products.[5-8] The potency of AMB-FUBINACA is consistent with strong CNS depressant effects that would account for the "zombielike" behavior of the users that was reported in this mass intoxication. Descriptions found on online drug forums (e.g., Reddit) regarding AMB-FUBINACA use terms such as "out of this world potent" with regard to its effects, which are described as being subjectively similar to those of Δ^9-THC.[28]

Despite the potential for overdose, increasingly potent synthetic cannabinoids may have become popular with drug dealers and users because of their low cost and potential for dilution into large volumes of product. A recent Internet query for purchase of AMB-FUBINACA powder showed prices of $1.95 to $3.80 per gram ($1,950 to $3,800 per kilogram). As shown in Table 1, the mean concentration of AMB-FUBINACA found in the packet recovered from the scene described in this report was 16.0 mg per gram. To obtain a 16-mg-per-gram product, a manufacturer could mix 1 kg of AMB-FUBINACA with 66.7 kg of plant material and produce approximately 15,625 packets, each containing 4 g of the product, with an online price averaging $35 per packet.

The absence of the parent compound, AMB-FUBINACA, in the biologic samples that were analyzed is typical for short-acting, potent psychoactive substances. For most esterified drugs, such as AMB-FUBINACA, hydrolysis occurs rapidly after intake, and the corresponding acid metabolites are detectable in biologic samples; the parent compound, however, may be detectable only at low levels.[29] For example, the only other serum value reported in the literature for any esterified indazole synthetic cannabinoid parent compound (5F-AMB, 0.19 ng per milliliter) is far below the range we observed for metabolites in biologic samples obtained in this outbreak.[30]

The concentration of AMB-FUBINACA metabolite observed in serum samples in this case series is similar to the range observed in samples from patients with intoxication caused by a different indazole synthetic cannabinoid (ADB-PINACA) that caused severe delirium in an outbreak in Georgia in 2013.[17] The severe behavioral alteration observed in the patients in New York City and reported by the press is consistent with the potent cannabinoid activity of AMB-FUBINACA; intoxication with this agent is unusual in that extreme CNS depression is not accompanied by the tachycardia, arrhythmia, seizures, hyperthermia, cardiotoxicity, and acute kidney injury that are usually found in association with potent or high doses of synthetic cannabinoid. In both the New York and the Georgia outbreaks, there may have been selection bias toward more severe cases because most of the samples analyzed were obtained from hospitals that received the most heavily intoxicated patients.

The cause of a cluster of serious intoxications by a new drug is usually not familiar to the medical community until it is first described in a case series. Identification of the responsible agent requires collaboration among clinical laboratories, health professionals, law enforcement agencies, and synthetic organic chemists so that

Table 2. Concentrations of the AMB-FUBINACA Acid Metabolite and Other Drugs Found in Samples from the Patients.*

Patient and Sample Type	Date Collected	Time Collected	AMB-FUBINACA Acid Metabolite Concentration	Other Drugs Detected
			ng/ml	
Patient A				
Serum	July 12	17:25	636	ND
Patient B				
Serum	July 12	13:35	232	Phenylpropanolamine
Patient C				
Serum 1	July 12	14:23	245	ND
Serum 2	July 13	04:30	155	Lorazepam
Urine	July 12	NA	165	Phenylpropanolamine
Patient D				
Serum	July 12	16:54	377	ND
Patient E				
Serum	July 12	NA	101	Mirtazapine, diphenhydramine
Urine 1	July 12	NA	<15	Mirtazapine, diphenhydramine
Urine 2	July 14	NA	<15	Mirtazapine, diphenhydramine
Patient F				
Serum	July 12	13:15	77	ND
Patient G				
Serum	July 12	19:30	159	Methadone
Patient H				
Whole blood	July 12	14:30	68	ND

* In serum samples from seven patients that were obtained at the time of the patients' presentation in the emergency department, the mean (±SD) concentration of AMB-FUBINACA acid metabolite was 247.8±183.2 ng per milliliter. A concentration of AMB-FUBINACA acid metabolite of 15 ng per milliliter was the lower limit of detection. NA denotes not available, and ND none detected.

timely information about the causative agent can be disseminated. The analysis of new psychoactive substances requires more than the typical targeted drug panels used in emergency departments and relies on more sophisticated analytic platforms that have the ability to rapidly identify previously unreported compounds. The clinical history provided by medical professionals aids in toxicologic analysis by eliminating well-characterized agents such as cocaine, heroin, and methamphetamine. The law enforcement agencies involved during an outbreak may be able to provide products and paraphernalia collected during mass intoxications for analysis. This may be especially important when very low concentrations of the drug or its metabolites are present in biologic samples. Finally, the ability to predict and rapidly generate reference standards for new drugs and their metabolites allows for the identification of previously unknown new psychoactive substances for which commercial reference standards are not available for many months after identification of the compound.[31] The collaborations in the current AMB-FUBINACA outbreak allowed for characterization of the responsible synthetic cannabinoid in only 17 days. As the number and complexity of new psychoactive substances increases, this type of coordination among multiple agencies is important for the timely resolution of future outbreaks.

The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Department of Homeland Security or its components or of the Drug Enforcement Administration.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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