Drug Early Warning from Re-Testing Biological Samples: Maryland Hospital Study

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Notice

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Abstract

The Community Drug Early Warning System (CDEWS) provides timely information about emerging drug use in criminal justice and patient populations in local communities by collecting and re-testing urine specimens already obtained and tested for a limited panel of drugs by local testing programs. CDEWS or local staff sample specimens that are ready to be discarded and send them to a collaborating laboratory for testing for an expanded panel of more than 160 drugs. By using already collected de-identified urine specimens, CDEWS can produce a relatively quick and inexpensive snapshot of the types of drugs recently used by participating populations and their testing program's ability to detect drugs being used by their population. The CDEWS methodology has been implemented in 15 sites and the results are contained in six reports already released by the Office of National Drug Control Policy.

This study of patients with a suspected synthetic cannabinoid (SC) overdose in two hospital emergency departments (EDs) is different from all prior CDEWS studies because: (1) this was the first CDEWS study of urine specimens obtained from patients in a hospital setting, and (2) de-identified patient medical record information was also collected for each patient and linked with their urinalysis result. The recent rise in Maryland of persons suffering adverse health consequences from the use of synthetic cannabinoids (SC), known as Spice or K2, underscored the need for this first CDEWS study of emergency department patients seen for a suspected SC overdose. The need for such a study was reinforced by our discussions with physicians from the two participating hospitals. This report presents findings from patients with a suspected synthetic cannabinoid overdose seen at two Maryland hospital EDs – Department of Emergency Medicine, University of Maryland Medical Center, Midtown Campus (UMMC) and the Emergency Department, Prince George's Hospital Center (PGHC). Neither of the on-site laboratories at these hospitals test patients' urines for possible use of SC as both hospitals utilize a limited testing panel of fewer than 10 drugs.

In 2016, a sample of 106 urine specimens was collected from PGHC and 69 specimens were collected from UMMC. Patient clinical information was also collected for each person for whom a urine specimen was obtained. These specimens were sent to the CDEWS collaborating laboratory and initially tested for a panel of 169 drugs, including 26 SC metabolites. However, when we unexpectedly found that all specimens but one tested negative for SC, we suspected that the patients had used even newer forms of SC not contained in our initial test panel. We therefore requested that our collaborating laboratory further expand the SC test panel to include additional newly available tests for specific SC metabolites. We then re-tested the specimens for SC using an updated panel of 46 SC metabolites.

Even with use of the updated panel, only about one-quarter of the specimens tested positive for SC. However, the specimens were found to contain a variety of other drugs, including marijuana and cocaine. PCP was found in 47 percent of the specimens from PGHC, and opioids, including both non-fentanyl (51%) and fentanyl opioids (28%), were detected in specimens from UMMC. These drug

use patterns are not surprising because PCP use is well documented in Prince George's County, the County in which PGHC is located, as well as in the neighboring city of Washington, DC. UMMC is located in Baltimore City, an area known to have a high prevalence of opioid use.

One-fifth to one-third of specimens at each hospital tested positive for a new psychoactive substance other than SC, with two cathinones, dibutylone and butylone, most commonly detected. We found that 33 percent of the specimens from patients at UMMC and 24 percent of those at PGHC contained three or more of eight selected likely illicit drugs or drug classes. For example, all 19 of the fentanyl positive specimens from UMMC contained another drug, and 14 of them contained six or more drugs or metabolites. These findings of multiple drugs detected in fentanyl-containing specimens are consistent with prior CDEWS studies. The presence of such a large variety of drugs, many in combination with one another, may have complicated the diagnosis of patients with an overdose involving SC.

Most of the SC positive specimens were found to contain only one or two SC metabolites, most often MDMB-FUBINACA metabolite M1. There was some variation, however, in the SC metabolites detected in each hospital, suggesting differences in the SC available in each locality. However, other drugs were detected in most SC positive specimens, with 96 percent of the SC positive specimens from PGHC and 86 percent of those from UMMC containing at least one drug in addition to SC.

The results from this study clearly demonstrate the complexity of both detecting and treating patients reporting to the ED for an adverse drug-related event. Only about one-fifth to one-quarter of specimens from each of the hospitals tested positive for SC even though these patients were being treated for a presumed SC-related overdose. The minority of patients for whom the treatment provider had a high level of certainty that they had used SC, as well as those patients who reported SC use and/or had a chief complaint related to SC, were significantly more likely to test positive for SC. However, SC was detected even among patients who did not report SC use, and many of the patients who tested negative for SC tested positive for other illicit drugs. Our findings do support the value of using emergency department patients' reports of drugs they have used. It should be noted, however, that few of the patients we studied reported use of the large variety of drugs they tested positive for. Physician knowledge of local drug use patterns may help physicians to anticipate drugs that are likely to have been used by their ED patients even though they may not have specifically disclosed them.

This first implementation of the CDEWS methodology in hospitals has demonstrated that CDEWS studies can be successfully adapted to hospital settings. Most of the challenges of conducting a CDEWS study in a hospital stemmed from our collection of additional clinical information on each subject, which may not be necessary for future CDEWS studies. Additional challenges, such as the availability of urine specimens for patients and the interpretation of results given that patients are

often administered medications in the emergency department, were unique to this setting and are discussed in this report.

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Introduction

The Community Drug Early Warning System (CDEWS) provides timely information about emerging drug use in criminal justice and patient populations in local communities by sampling and re-testing urine specimens already obtained and tested for a limited panel of drugs by local testing programs. CDEWS or local staff sample the specimens that are ready to be discarded and send them de-identified to a collaborating laboratory for testing for an expanded panel of drugs. By using already collected de-identified urine specimens, CDEWS can provide a relatively quick and inexpensive snapshot of the types of drugs recently used by participating populations (see Appendices A and B for more details on the CDEWS methodology). The CDEWS has two primary objectives: (1) to identify and describe the use of emerging drugs in populations at high risk for recent drug use; and (2) to specify any important drugs that the current local testing program may be missing. A major innovation in the CDEWS methodology used in the current study is the expansion of the CDEWS testing panel to include testing for more than 160 licit and illicit substances, including opioids, benzodiazepines, antidepressants, and new psychoactive substances (NPS), using more sensitive testing technology than is typically available to local testing programs.

The CDEWS results from criminal populations are especially important for detecting emerging drugs because prior epidemics in the use of illegal drugs have often shown up in urinalysis results from criminal justice populations before they have become evident in the larger community (DuPont & Wish, 1992; Wish, 1997). Tests of specimens obtained from patient populations can also provide an indication of the drugs causing adverse health consequences. Local testing programs typically can test for only a small number (often 6-12) of different drugs and the CDEWS results for more than 160 substances can be used by the local testing programs to gain some insight into whether their standard more limited test panel is adequate for identifying most of the drugs being used by their testing population.

The CDEWS methodology has now been piloted in 15 sites and the results are provided in six reports already released by the Office of National Drug Control Policy (ONDCP) (Billing et al., 2017; Wish et al., 2013, 2015, 2016, 2016a, 2017). This study of patients with a suspected synthetic cannabinoid overdose in two hospital emergency departments is different from prior CDEWS studies because: (1) this was the first CDEWS study of urine specimens from patients in a hospital setting, and (2) de-identified patient medical record information was also collected for each patient and linked with their urinalysis result. This report provides results for patients from two participating Maryland hospital emergency departments – the Emergency Department at the Prince George's Hospital Center (PGHC) and the Department of Emergency Medicine, University of Maryland Medical Center, Midtown Campus in Baltimore (UMMC).

Methodology

Site Selection Procedures

The recent rise in Maryland of persons suffering adverse health consequences from the use of synthetic cannabinoids (SC) (Bensen & Swalec, 2015; Hauslohner & Hermann, 2015; Thompson, 2015), known as Spice or K2, underscored the need for this first CDEWS study of emergency department patients seen for a suspected SC overdose. The need for such a study was reinforced by our discussions with physicians from the two participating hospitals. We sought adult patients seen at either of two Maryland hospital emergency departments - the Emergency Department at the Prince George's Hospital Center (PGHC) and the Department of Emergency Medicine at the University of Maryland Medical Center, Midtown Campus (UMMC) between January and October 2016. Neither of the on-site laboratories at these hospitals test patients' urines for possible use of SC as both hospitals utilize a limited testing panel of fewer than 10 drugs. Prior to data collection, the Center for Substance Abuse Research (CESAR) at the University of Maryland, College Park, which carried out this study, obtained approval for the research from both the University of Maryland, College Park's Institutional Review Board (IRB) and each hospital's Institutional Review Board. The specific steps taken to recruit and work with these sites are described in Appendix A, and more details about the specimen collections contained in Appendix B. Table 1 provides descriptions of the two participating hospitals.

Urinalyses of patients presenting to the emergency department with a suspected drug overdose are conducted by the participating hospitals in most cases, when possible. However, neither of the toxicology panels used by the participating hospitals include any synthetic drug compounds, such as SC, given that they utilize a limited drug testing panel. The onsite laboratory panel for PGHC screens for eight drugs: amphetamines, barbiturates, benzodiazepines, cocaine, marijuana, methadone, opiates, and PCP (see Table 1). The UMMC onsite laboratory panel screens for seven drugs: amphetamine, barbiturates, benzodiazepines, cocaine, marijuana, opiates, and PCP. Tests for methadone and buprenorphine at UMMC can be ordered upon special request (see Table 1).

Table 1: Description of the Participating Study Sites

Site	Populations Covered	Type of Laboratory	Drugs in Standard Hospital Screen	Targeted Number of Specimens to be Collected for CDEWS
Emergency Department, Prince George's Hospital Center	Emergency Department patients with a suspected SC overdose	On-site laboratory screening	8-panel screen: amphetamines, barbiturates, benzodiazepines, cocaine, marijuana, methadone, opiates, and PCP.	100 specimens
Department of Emergency Medicine, University of Maryland Medical Center, Midtown Campus	Emergency Department patients with a suspected SC overdose	On-site laboratory screening	7-panel screen: amphetamines, barbiturates, benzodiazepines, cocaine, marijuana, opiates, and PCP. Methadone and buprenorphine can be ordered upon request.	100 specimens

Patient Eligibility and Enrollment

Patient eligibility for the study was determined by collaborating physicians at each participating hospital using a patient eligibility screener (see Figures B-1 and B-2). Patients were eligible for the study for any of three reasons: (1) the patient exhibited agitation due to suspected SC use or undefined cause; (2) there was evidence of SC use (e.g., self-report, paraphernalia, police/EMS/bystander report of SC use, MD/RN suspicion, etc.); and/or (3) if the patient had a chief complaint related to SC. These eligibility criteria were assessed by the emergency department (ED) physicians enrolling patients in the study through a variety of mechanisms, including (1) direct patient observation, (2) information provided by the patient's attending physician or other source (such as police, EMS, etc.), and/or (3) review of the patient's medical record. While the physicians enrolling patients in the study made every attempt to enroll known or suspected SC users, some patients were enrolled by the ED physicians when agitation was present that was suspected to be related to use of an unknown drug. During the period of the study, many of these patients with agitation were suspected to be using SC because of its known prevalence in Maryland at the time (Bensen & Swalec, 2015; Hauslohner & Hermann, 2015; Thompson, 2015). Other eligibility criteria were that the visit be the patient's first visit to the hospital since the start of the study (to avoid enrolling duplicate persons in the study) and that a urine specimen of adequate volume (10mL or more) was available for the patient.

We targeted for collection a total of 100 urine specimens and patient information from unduplicated adult emergency department patients with a suspected SC overdose at each hospital (total of 200 specimens). For each eligible patient, a urine specimen and medical information from

their records were obtained and provided to CESAR in de-identified form. More details regarding the data collection are provided in Appendix B.

Sampling of Urine Specimens and Collection of Patient Medical Information

Prior to sampling the urine specimens, CESAR staff talked with collaborating staff from both hospitals by phone to determine their policies regarding specimen holding periods, testing protocols, detection limits and other relevant site details. Existing urine specimens were obtained and patient record information was collected by collaborating hospital emergency department physicians using specific CDEWS guidelines developed by CESAR. A non-identifiable study ID was used to link the urine specimens and patient record data for the study. CESAR staff conducted on-site visits at each hospital several times throughout the study to prepare the urine specimens for shipment to the CDEWS collaborating laboratory for expanded drug testing. The completed de-identified patient medical information forms were also collected by CESAR staff at each site visit. Additional details of the specimen selection appear in Appendix B.

Interviews with Toxicologists to Develop the CDEWS Testing Panel

In the prior CDEWS studies, we had learned that both the chemical composition of synthetic drugs available and patterns of use can vary widely even within a brief period of time. It is a recognized challenge for both laboratories and law enforcement to keep up with the rapid changes in the composition of synthetic drugs. The chemists producing these drugs modify the chemical structures of the drugs as existing formulations are scheduled by the DEA and made illegal. To ensure that the drug test panel was as current as possible and included the most relevant drugs/metabolites, CESAR staff reviewed data on emerging drug trends and conducted interviews with toxicologists and other relevant professional contacts to identify substances for inclusion on the expanded test panel. Additional information on the data reviewed and persons interviewed appears in Table C-1 in Appendix C.

Based on the above information, we asked the CDEWS laboratory to add 26 new psychoactive substances (NPS) to our previous CDEWS-3 designer drug screen. The total number of drugs tested for increased from 153 to 169 (after a few rare drugs were dropped from the panel) and included 26 SC metabolites (see Table C-2 in Appendix C for the full test panel). What proved to be an important limitation to our approach was that we had identified several SC metabolites that could not be included in the test panel because reference standards for urine testing were not available at the time specimen testing commenced.

Need to Re-test Specimens for SC

All specimens were initially tested by the CDEWS collaborating laboratory, the Armed Forces Medical Examiner System (AFMES) Laboratory located in Delaware, for the expanded drug testing panel in November-December 2016. These specimens were tested for a panel of 26 SC metabolites, 59 designer stimulants, and 84 other illicit and prescription drugs. We unexpectedly found that all

specimens but one tested negative for SC. We suspected that maybe the patients had used even newer forms of SC that were not contained in our test panel. We therefore requested that AFMES further expand the SC test panel to include additional newly available tests for specific SC metabolites. Approximately one year later, in November 2017, the SC testing panel was updated to include 46 SC metabolites. The following test results for SC are based on the updated panel (Table C-3 in Appendix C compares the specific SC metabolites included in the initial and re-test panels).

Results

We first describe the specimens collected, some demographic characteristics about the patients who provided them and the reasons these persons were enrolled in the study. A description of how patients were brought into the emergency department, their chief complaint, and their mental status are then presented. We next describe the CDEWS drug test results and a set of special analyses about the patients who tested positive for SC. Some drugs were recorded as having been administered by emergency department staff to patients in the study and/or prescribed by a physician prior to the patient's hospital visit. This included drugs such as prescription opioids, benzodiazepines, antidepressants, and other prescription drugs. In cases where the patient tested positive for one or more of these drugs and the patient record indicated that the drug(s) was either administered and/or prescribed to the patient, the patient's test result for the drug(s) was counted as negative in all analyses. Additional analyses of the patient symptom information and clinical test results was beyond the scope of the present project and will be part of a later study.

Emergency Department Patients, Prince George's Hospital Center

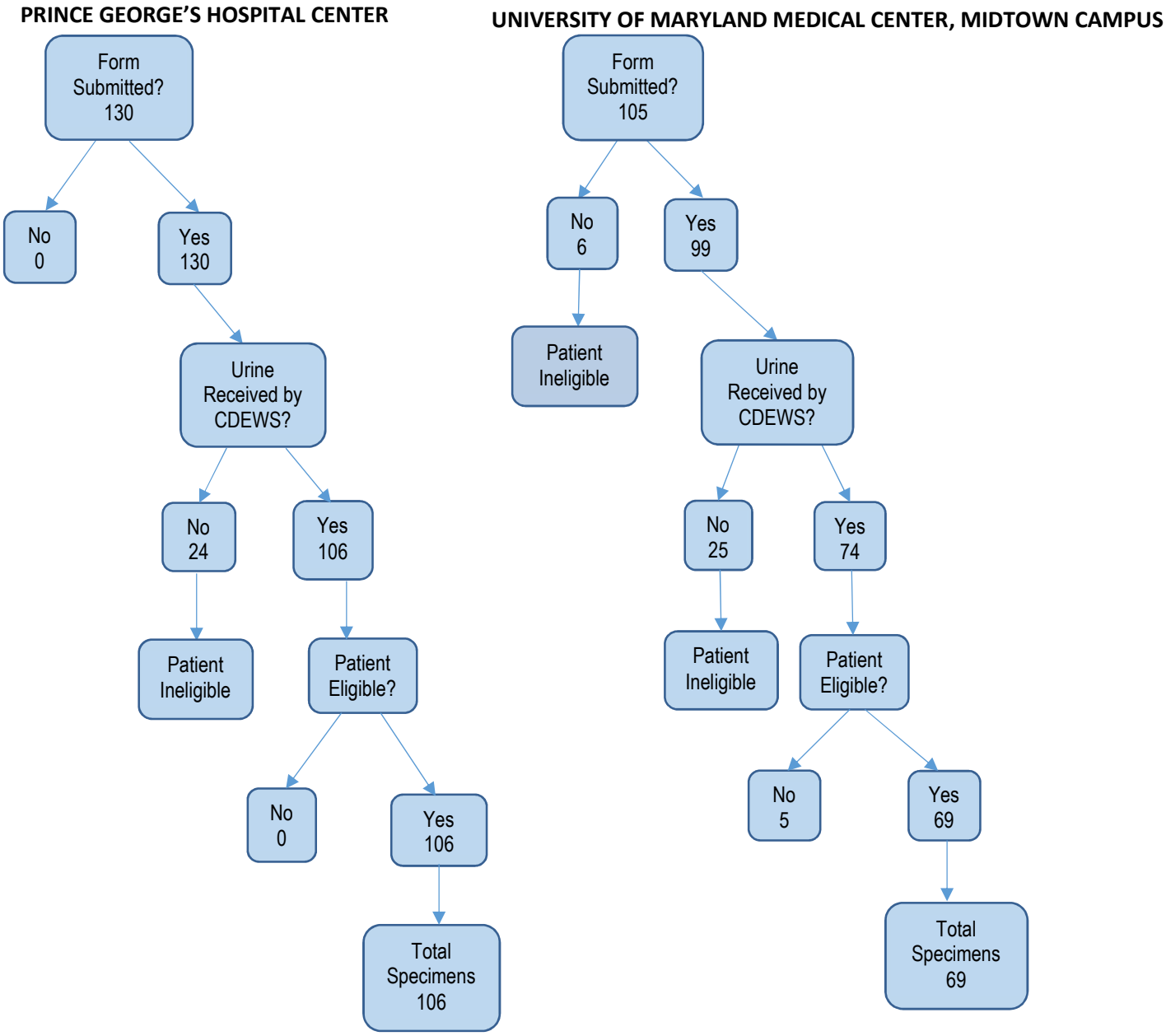
Specimens were collected between January and October, 2016. We had targeted 100 specimens and received a total of 106 specimens from patients that were eligible for inclusion in the study. The final sample included one patient for whom an eligibility form was incomplete but the provider's certainty regarding the patient's SC use was rated 5 on a 5-point scale. A total of 130 patient information forms were submitted, however, 24 persons were omitted from the analysis because a urine specimen was not received (Figure 1).

Emergency Department Patients, University of Maryland Medical Center, Midtown Campus

Specimens were collected between February and September 2016. We had targeted 100 specimens but received a total of 69 specimens from patients that were eligible for inclusion in the study. Eleven persons for whom urine specimens were collected were omitted from the analysis for this site (see Figure 1). These included six patients for whom no patient form was received and five patients who were ineligible due to incomplete eligibility information. An additional 25 persons were omitted from the analysis because no urine was received.

All subsequent analyses are based on the 106 patients from PGHC and the 69 patients from UMMC for whom urine specimens and patient information were received.

Figure 1: Data Collected From Each Site



A. Demographic Characteristics of Enrolled Persons

Table 2 presents some demographic characteristics of the enrolled persons. The patients at PGHC were somewhat younger, with 70 percent ages 35 or younger, compared to 49 percent of the patients at UMMC. Almost one-quarter (23%) of the patients at UMMC were aged 51 or older, compared to only seven percent at PGHC. Approximately three-quarters of the patients or greater were African-American males and almost all were of Non-Hispanic ethnicity.

Table 2: Demographic Characteristics of Emergency Department Patients, By Site

(N=175 patients)

	Prince George's Hospital Center (N=106) %	UMMC, Midtown Campus (N=69) %
Age^		
25 or younger	31% (70%)	25% (49%)
26 to 35	39	24
36 to 40	16	15
41 to 50	7	13
51 or older	7	23
Total	100%	100%
Gender		
Male	76%	87%
Female	24	13
Total	100%	100%
Race^		
Black/African-American	93%	77%
Caucasian	6	22
Other	1	1
Total	100%	100%
Ethnicity^Δ		
Non-Hispanic	96%	100%
Hispanic/Latino	4	0
Total	100%	100%

Notes:
^N's vary slightly because of missing demographic information.
ΔEthnicity was not reported for 46 persons from the UMMC, Midtown Campus site.

B. Reasons for Patient Enrollment in the Study

Table 3 shows the reasons why patients were enrolled in the study. Hospital enrolling physicians could indicate on the data collection form multiple reasons for why they enrolled a patient. Because multiple reasons could have been selected, the numbers in Table 3 total to more than 100 percent. Almost three-quarters of the patients in each group had exhibited evidence of SC use based on either the patient's self-report, paraphernalia, and/or the nurse/physician or others' observations. Another common reason was agitation due to suspected SC use, use of another drug, or other undefined cause (45-49%). For about one-fifth of the patients, the treatment provider was extremely certain the patient had used SC (scored 5 on a five point scale of certainty). Fifteen percent or fewer patients had a chief complaint related to SC use. All of the patients enrolled from each hospital had at least one of these reasons for enrollment. We also analyzed this data excluding Reason 2, agitation due to SC or an undefined cause, since some of those patients could have been enrolled for causes other than SC use. However, even when Reason 2 was omitted, almost 80 percent of patients still had one of the other reasons. Taken together, these results indicate that patients enrolled from both emergency departments were viewed as having an SC-related health problem.

Table 3: Reason Why Patient Was Enrolled in Study, By Site

	Prince George's Hospital Center Emergency Department (N=106) %	**UMMC, Midtown Campus Emergency Department** (N=69) %
Reason		
1. Evidence of SC use	74%	70%
2. Agitation due to suspected SC use or other undefined cause	49	45
3. Treatment provider certain that patient used SC*‡	22	20
4. Chief complaint related to SC	8	15
Any of the above 4 reasons	100%	100%
Any of the above reasons (excluding reason 2)	79%	78%

*Treatment provider's certainty of synthetic cannabinoid use was 5 (on a 5-point scale) on patient form.
‡N's for this row vary slightly due to missing information.

C. How Patients Arrived at the Hospital and Presenting Problems

Table 4 shows that 78 percent of the patients at PGHC and 90 percent at UMMC were brought to the emergency department by police or EMS. A small percentage (20% and 10%, respectively) came in on their own. There were some significant differences in the chief complaints reported for the patients from the two hospitals. The patients in PGHC were twice as likely to have had an Emergency Petition (also known as Emergency Petition Service/EPS and defined as the involuntary detainment of an individual for psychiatric evaluation) or a psychiatric event (43% vs 20%, $p<.01$). PGHC patients were also three to four times more likely to show bizarre or aggressive behavior. The UMMC patients were more likely to present as drug overdose or poisoning (26% vs. 6%, $p<.001$). One-fourth to one-third of patients from both groups showed physiological symptoms and smaller numbers showed altered mental status, psychological symptoms, or were found down (unconscious).

Emergency Department staff members were able to indicate on the research form additional information about a patient's physiological symptoms, aggressive behavior, and bizarre behavior. Some common examples of physiological symptoms included chest pain, racing heart beat/palpitations, intoxication, and unresponsiveness. Examples of aggressive behavior were agitation, threats or violent behavior towards family members, and combativeness. Some examples of bizarre behavior included walking in traffic/wandering down the streets, trying to bite people, incomprehensible words, lying in someone's yard, and hallucinating/hearing voices.

The most common mental status on admission was patient agitation or being anxious. Agitation was more common in patients at PGHC (53% vs. 36%, $p<.05$). On a smaller number of research forms (as this item was added later in the study), physicians were also given the option to specify an "other" mental health status for the patient. These responses were then grouped by research staff into thematic categories. The most commonly recoded category was that the patient was lethargic or unresponsive. Lethargic or unresponsive comprised the largest subset of patients with the "other" option in both hospitals. Fluctuating mental status and/or hallucinations were reported in a small minority of patients from both hospitals.

Our description of the two groups of participating patients has uncovered some significant differences in the patients from the two hospitals. While most participants from both hospitals sought or were brought to the emergency department for a presumed health problem related to their use of SC, the UMMC patients were older, less agitated, and were more likely to report a chief complaint of an overdose or drug poisoning. The PGHC patients were more likely to be at the hospital because of an Emergency Petition, and had exhibited bizarre or aggressive behavior. Given these differences, the next section examines whether the patients from the two hospitals tested positive for different drugs.

Table 4: How Patients Arrived at the Hospital and Presenting Problems

	Prince George's Hospital Center Emergency Department (N=106) %	UMMC, Midtown Campus Emergency Department (N=69) %
Brought in by§		
EMS/Police	78*	90*
Walk-in/Self-referral	20	10
Chief Complaints△		
Emergency Petition Service^/Psych	43%**	20%**
Physiological Symptom	28	32
Aggressive Behavior	24**	6**
Bizarre Behavior	21*	7*
Altered Mental Status (AMS)	18	12
Psychological Symptom	13	4
Found down	7	15
Overdose (OD)/Poisoning	6***	26***
Mental Status on Arrival†		
Agitated	53%*	36%*
Anxious	41	30
Lethargic or unresponsive	(n=70) 14‡	(n=46) 30‡
Fluctuating	12	7
Hallucinating	10	4

Note: This table includes only categories reported in 10% or more of cases at either site.

§The response category "Other" was excluded from 'Brought in by' because it accounted for <10% of cases at either site.

△The response categories of "Suicidal Ideation/Attempt", "Driving Incident", "Victim of Violent Crime/Trauma", "Fall", "Pedestrian-Struck", and "Other" were excluded from 'Chief Complaints" because they accounted for <10% of cases at either site. Some of these response categories were established after thematically grouping responses collected as part of the "Other, specify" category.

^Emergency Petition Service (EPS) is a service that, under specific conditions, allows for an individual to be involuntarily detained for a psychiatric evaluation.

†The response categories of "Suicidal or homicidal ideation", "Violent behavior", "Abnormal involuntary movements", "Flat affect", "Disoriented", and "Intoxicated" were excluded from 'Mental Status on Arrival' because they accounted for <10% of cases at either site. Some of these response categories were established after thematically grouping responses collected as part of the "Other, specify" category.

‡N's for this item were low due to this question being added later in the study.

*p<.05 by Chi Square.
**p<.01 by Chi Square.
***p<.001 by Chi Square.

D. Drugs Detected by the CDEWS Collaborating Laboratory

The test results in Table 5 were unexpected. Only 23 percent of the specimens from patients at PGHC and 20 percent of those from UMMC tested positive for SC, even though these persons had entered their emergency departments for a suspected SC related problem. Even after we excluded the persons enrolled in the study for agitation from an unknown cause (see Table 3, reason #2), we found that the percentage testing positive for SC only increased to about 24 percent in each hospital. On the other hand, these specimens were found to contain a variety of other drugs, many in combination with one another, that had likely caused their symptoms. This section describes the drugs found in patients from each hospital separately and then compares the pattern of test results from the two hospitals. In this report, the term " Any NPS" excludes the following New Psychoactive drugs: synthetic cannabinoids and synthetic fentanyl analogues, which appear separately in our tables.

Prince George's Hospital Center

The most common individual drugs detected were marijuana (69%), followed by PCP (47%), and cocaine (22%). As noted above, only 23 percent of specimens tested positive for SC, primarily MDMB-FUBINACA metabolite M1. A more in-depth analysis of the SC findings is presented in the next section. A new psychoactive substance (NPS) other than SC was detected in 22 percent of the specimens. The three most frequently detected NPS were dibutylone (9%), butylone (9%), and mCPP (8%). Trazodone is an anti-depressant for which mCPP is its major active metabolite. It is not possible to know definitively whether mCPP was present because of trazodone use or because it was taken separately. However, all eight of the specimens positive for mCPP also contained trazodone. Any fentanyl (4%) and any non-fentanyl opioids (12%) were rarely detected in these specimens.

University of Maryland Medical Center, Midtown Campus

The most common individual drugs found were marijuana (61%), followed by cocaine (46%). In addition, 51 percent of the specimens tested positive for a non-fentanyl opioid, mainly morphine (38%), codeine (26%), and 6-monoacetylmorphine, a metabolite of heroin (6-MAM, 13%). Fentanyl or its analogues were also found in 28 percent of specimens, typically fentanyl/norfentanyl (25%) and 4-ANPP (despropionyl fentanyl, 19%). Only one-fifth (20%) of the specimens were found to contain SC, most of which tested positive for MDMB-FUBINACA metabolite M1. Benzodiazepines were detected in 33 percent of the specimens, mainly alprazolam/α-hydroxyalprazolam (20%). Nearly one-third of specimens tested positive for an NPS other than SC, most commonly dibutylone (22%) and butylone (17%). Naloxone was detected in 25 percent and may have been administered in the ED or by EMS or others at the scene of the overdose; quinidine/quinine (26%) is sometimes mixed with heroin.

Comparison of Test Results from PGHC and UMMC

Patients from both hospitals had relatively similar test results for the presence of marijuana, Any SC, and Any Antidepressants. However, it is clear from the results that PCP was primarily found in patients from PGHC (47% vs 3%, p<.001). On the other hand, cocaine, fentanyl, non-fentanyl opioids, and benzodiazepines were much more common among patients from UMMC. Butylone and dibutylone were also found in a minority of patients from both hospitals, but dibutylone was twice as common in patients in UMMC, (22% vs 9%, p<.05). We conclude that while about similar percentages of both groups of patients had used SC and marijuana, they differed primarily in their use of PCP, benzodiazepines, and opioids.

Some of the opioids we detected (buprenorphine, methadone and the pharmaceuticals) could have been used under a doctor's supervision. Table 6 therefore provides a comparison of just the likely illicit drugs that would not be used under a doctor's supervision that were detected in the two groups. We found that 91 percent of the PGHC patients and 94 percent of the UMMC patients tested positive for one or more of the eight drugs or drug classes in Table 6. When we excluded marijuana, the percentages dropped to 74 percent and 75 percent, respectively. Specimens from PGHC contained an average of 1.9 drugs or drug classes and those from UMMC contained an average of 2.1 drugs or drug classes. One third of the specimens from patients at UMMC and approximately one-quarter (24%) of those at PGHC contained three or more drugs or drug classes (see Table 6).

Our prior research (CESAR, 2017, 2017a; Wish et al., 2017) has shown that fentanyl positive specimens often test positive for multiple drugs. The 19 specimens in the UMMC population that tested positive for fentanyl or its metabolite were sufficient to enable us to describe the other drugs found in these specimens. Table 7 shows that all of these specimens contained at least one other drug, and 14 of the 19 specimens contained six or more drugs or metabolites. Morphine (a metabolite of heroin/codeine found in 95%), cocaine (74%), and codeine (68%) were the drugs most commonly found in these fentanyl positive specimens. One of these specimens contained only one other drug, naloxone, which might have been administered in the ED or by first responders or others at the scene of the overdose.

Table 5: CDEWS Laboratory Test Results for Emergency Department Patients, by Hospital Site

(N=175 specimens collected between January 2016 and October 2016)‡

Percent Positive by CDEWS Lab for:	Prince George's Hospital Center§ (N=106) %	UMMC, Midtown Campus^ (N=69) %
Marijuana	69	61
Cocaine	22**	46**
PCP	47***	3***
Methadone/EDDP	<1***	19***
Methamphetamine	3	3
Amphetamine	0	1
Any Non-Fentanyl Opioid	12***	51***
Morphine△	7***	38***
Codeine△	<1***	26***
6-Monoacetylmorphine (6-MAM)	0***	13***
Hydromorphone△	3	7
Oxymorphone	4	3
Buprenorphine/Norbuprenorphine△	0**	7**
Oxycodone△	3	3
Tramadol△	<1	4
Hydrocodone△	<1	0
Any Fentanyl	4***	28***
Fentanyl/Norfentanyl△	<1***	25***
4-ANPP (Despropionyl fentanyl)	2***	19***
Furanylfentanyl	<1*	9*
Acetylfentanyl	0*	6*
Parafluorobutyryl fentanyl	0	4
Parafluorofentanyl	<1	1
Any New Psychoactive Substance (NPS)	22	32
Dibutylone	9*	22*
Butylone	9	17
mCPP†	8	10
Methylone	4	4
Ethylone	3	4
Dimethylone	2	4
Eutylone	<1	1
β-Methylphenethylamine	0	1
Pentylone	0	1
α-PVP	<1	0

5-APDB/6-APDB	<1	0
Any Synthetic Cannabinoid (SC)	23	20
MDMB-FUBINACA metabolite M1 (Re-test only)	16	20
MMB-FUBINACA (Re-test only)	9	1
5F-AMB metabolite 7 (Re-test only)	7*	0*
FUB-PB-22 3-carboxyindole metabolite (Re-test only)	0	4
5F-ADB metabolite 7 (Re-test only)	2	0
5F-PB-22 3-carboxyindole	2	0
JWH-073-N-COOH	2	0
ADB-FUBINACA (Parent)	0	1
AB-CHMINACA (metab 4)	<1	0
BB-22 3-carboxyindole	<1	0
PB-22 3-carboxyindole	<1	0
Any Benzodiazepine	11***	33***
Alprazolam/α-Hydroxyalprazolam$^{\Delta}$	<1***	20***
Oxazepam$^{\Delta}$	3	7
α-Hydroxymidazolam	4	4
Temazepam	2	7
Demoxepam	2	6
Diazepam/Nordiazepam$^{\Delta}$	3	4
Clonazepam/7-Aminoclonazepam$^{\Delta}$	<1	4
Lorazepam$^{\Delta}$	<1	4
Flurazepam/Desalkflurazepam	<1	1
Estazolam	0	1
Flunitrazepam	<1	0
Any Antidepressant	13	19
Trazodone$^{\Delta\dagger}$	9	10
Citalopram$^{\Delta}$	2	4
Fluoxetine$^{\Delta}$	<1	3
Venlafaxine	0	3
Nortriptyline	<1	1
Amitriptyline	0	1
Desvenlafaxine	0	1
Doxepin	0	1
Sertraline$^{\Delta}$	<1	0
Other Drugs		
Naloxone$^{\Delta}$	6***	25***
Quinidine/Quinine	0***	26***
Cetirizine	5**	17**
Haloperidol$^{\Delta}$	9	10
Dextromethorphan	9	1

Hydroxyzine	2*	10*
Promethazine[Δ]	<1*	7*
Cyclobenzaprine[Δ]	3	3
Ketamine/DHNK	0*	6*
Loperamide	3	1
Chlorpromazine[Δ]	0	1
Zolpidem	0	1
LSD	<1	0
Methylphenidate	<1	0

[‡]Specimens from the Prince George's Hospital Center Emergency Department were collected between January 2016 and October 2016. Specimens from the University of Maryland Medical Center, Midtown Campus, Emergency Department were collected between February 2016 and September 2016.

[§]Prince George's Hospital Center Emergency Department patients with a suspected synthetic cannabinoid overdose were tested for a panel of eight drugs, including: amphetamines, barbiturates, benzodiazepines, cocaine, marijuana, methadone, opiates, and PCP.

[^]University of Maryland Medical Center, Midtown Campus, Emergency Department patients with a suspected synthetic cannabinoid overdose were tested for a panel of seven drugs, including: amphetamine, barbiturates, benzodiazepines, cocaine, marijuana, opiates, and PCP. Methadone and buprenorphine were tested upon request.

[†]Trazodone is an antidepressant whose major active metabolite is mCPP. It is not possible to definitively determine whether the presence of mCPP was due to Trazodone use or whether mCPP was taken on its own.

[Δ]It is not possible to definitively determine whether the presence of these drugs were due to illicit use or whether drugs were administered or prescribed by a physician; however, drug test results with evidence of the drug being administered to the patient by emergency department staff or evidence of patient taking the drug by prescription were counted as negative in this analysis.

*p<.05 based on Fisher's Exact Test or Chi Square.

**p<.01 based on Fisher's Exact Test or Chi Square.

***p<.001 based on Fisher's Exact Test or Chi Square.

Table 6: Percentage Positive for Likely Illicit Selected Drugs, By Site

(N=175 specimens collected between January 2016 and October 2016)‡

Positive by CDEWS Lab for:	Prince George's Hospital Center (N=106) %	UMMC, Midtown Campus (N=69) %
1. Marijuana	69	61
2. Cocaine	22**	46**
3. PCP	47***	3***
4. Any New Psychoactive Substance (NPS)	22	32
5. Any Synthetic Cannabinoid (SC)	23	20
6. Any Fentanyl[Δ]	4***	28***
7. 6-Monoacetylmorphine (6-MAM)	0***	13***
8. Methamphetamine	3	3
Positive for Any (of 8)	91%	94%
Positive for Any (excluding marijuana)	74%	75%
Number of Drugs/Drug Classes in Specimen (of 8):		
0	9	6
1	28	29
2	39	32
3	14	22
4	8	10
5	<1 (24%)	1 (33%)
6	<1	0
Total:	100%	100%
Mean Number of Drugs Found Positive (of 8):	1.89	2.06

Note: LSD and Amphetamine were excluded from this data.

‡Specimens from the Prince George's Hospital Center Emergency Department were collected between January 2016 and October 2016. Specimens from the University of Maryland Medical Center, Midtown Campus, Emergency Department were collected between February 2016 and September 2016.

[Δ]It is not possible to definitively determine whether the presence of these drugs were due to illicit use or whether drugs were administered or prescribed by a physician; however, drug test results with evidence of the drug being administered to the patient by emergency department staff or evidence of patient taking the drug by prescription were counted as negative in this analysis.

**p<.01 based on Chi Square.

***p<.001 based on Fisher's Exact Test or Chi Square.

Table 7: Other Drugs Detected in 2 or More Cases of Fentanyl Positive* Specimens

(N=19 Fentanyl Positive specimens from UMMC, Midtown Hospital)^

	Opioids						Illicit Non-Opioid Drugs						Pharmaceutical Non-Opioid Drugs									
Specimen	Morphine$^{\Delta}$	Codeine$^{\Delta}$	Methadone/EDDP	6-Monoacetylmorphine (6-MAM)	Buprenorphine/ Norbuprenorphine$^{\Delta}$	Hydromorphone$^{\Delta}$	Cocaine	Marijuana	Dibutylone	Butylone	mCPP†	Methamphetamine	Naloxone$^{\Delta}$	Cetirizine	Alprazolam/ α-Hydroxyalprazolam$^{\Delta}$	Trazodone$^{\Delta\dagger}$	α-Hydroxymidazolam	Hydroxyzine	Promethazine$^{\Delta}$	7-Aminoclonazepam/ Clonazepam$^{\Delta}$	Citalopram$^{\Delta}$	Total # of Drugs/ Metabolites Detected‡
1	✓	✓	✓	✓	✓		✓	✓					✓	✓	✓		✓	✓				12
2	✓	✓	✓	✓			✓	✓				✓	✓	✓			✓	✓				11
3	✓	✓		✓					✓	✓	✓		✓	✓	✓	✓						10
4	✓	✓	✓	✓			✓							✓	✓		✓	✓				9
5	✓	✓	✓			✓	✓	✓							✓				✓	✓		9
6	✓	✓			✓		✓	✓					✓		✓	✓						8
7	✓		✓				✓						✓		✓				✓	✓	✓	8
8	✓		✓			✓	✓						✓		✓				✓			7
9	✓	✓	✓				✓								✓	✓					✓	7
10	✓	✓			✓				✓	✓			✓									6
11	✓	✓		✓			✓	✓					✓									6
12	✓	✓					✓		✓				✓	✓								6
13	✓	✓	✓	✓			✓							✓								6
14	✓	✓					✓	✓				✓		✓								6
15	✓	✓		✓				✓								✓						5
16	✓						✓	✓						✓								4
17	✓								✓	✓	✓											4
18	✓						✓		✓													3
19													✓									1
Total	18	13	8	7	3	2	14	8	5	3	2	2	10	8	8	4	3	3	3	2	2	128

*Includes specimens positive for any fentanyl compound on the testing panel. Fentanyl compounds detected: 4-ANPP (despropionyl fentanyl), acetylfentanyl, fentanyl, furanylfentanyl, norfentanyl, parafluorobutyryl fentanyl, and parafluorofentanyl.

^Includes drugs detected in 2 or more of the 19 fentanyl positive specimens. The following drugs were found in only 1 fentanyl positive specimen: Amphetamine, β-Methylphenethylamine, Desalkflurazepam, Dextromethorphan, Doxepin, Estazolam, Fluoxetine, Haloperidol, Ketamine/DHNK, Loperamide, Lorazepam, MDMB-FUBINACA metabolite M1, Nordiazepam, Oxazepam, PCP, Temazepam, and Tramadol. Quinidine/Quinine was detected in 84% of specimens but is excluded from this table.

†Trazodone is an antidepressant whose major active metabolite is mCPP. It is not possible to definitively determine whether the presence of mCPP was due to Trazodone use or whether mCPP was taken on its own.

$^{\Delta}$It is not possible to definitively determine whether the presence of these drugs were due to illicit use or whether drugs were administered or prescribed by a physician; however, drug test results with evidence of the drug being administered to the patient by emergency department staff or evidence of patient taking the drug by prescription were counted as negative in this analysis.

‡Two or more of the drugs may have been detected as a result of taking one substance.

E. Special Analyses of Synthetic Cannabinoid Use

Because this study focused on patients believed to have gone to the emergency department because of an SC related negative health consequence, we conducted several analyses that focused on the patients who tested positive for SC.

Age

Table 8 shows the mean ages of persons who tested positive for selected drugs. In prior CDEWS studies of criminal populations (Wish et al., 2013, 2015), persons who tested positive for SC, PCP, and marijuana tended to be among the youngest persons studied. However, the UMMC patients were on average six years older than those from PGHC (37.2 years vs. 31.2, $p<.01$). The older patients from UMMC, together with the fact that these were all patients treated in the ED rather than persons under criminal justice supervision, likely influenced the associations in Table 8. For both hospitals, persons testing positive for marijuana were the youngest, (29.4 at PGHC and 33.1 years at UMMC). However, PGHC patients testing positive for PCP (34.5) or any SC (35.8) were among the oldest average ages of all those studied in that hospital. Except for marijuana, the patients at UMMC who tested positive for other drugs were all in a narrow, older age range (38.1-44.5 years). UMMC patients who tested positive for SC, while among the youngest, were still a mean age of 38.1 years old. Perhaps SC use by older persons results in more health consequences causing them to enter the hospital.

Number of SC metabolites in SC positive specimens

Several of the prior CDEWS studies found multiple SC metabolites in specimens testing positive for any SC (Billing et al., 2017; Wish et al., 2015, 2017). Table 9 shows that this was not true for these ED patients. One-half of the SC positive specimens from PGHC and 64 percent of those from UMMC tested positive for only one SC metabolite. Two metabolites were detected in 29 percent of the 24 SC positive specimens from PGHC and in 36 percent of the 14 SC positive specimens from UMMC. Only a small percentage of specimens (21%) from PGHC were positive for three or more metabolites, with specimens from UMMC showing no more than two metabolites. MDMB-FUBINACA metabolite M1, a new metabolite added in the latest update of the SC panel, was detected in the large majority of the SC positive specimens from both hospitals. This metabolite was found in all of the SC positive specimens from UMMC and explains why we did not find any SC in UMMC specimens in our initial tests conducted prior to adding this metabolite. It is notable that there was significant variation in the SC metabolites detected in each hospital, suggesting regional differences in the SC available in each locality.

Number of other drugs found in SC positive specimens

Tables 10 and 11 show the other drugs identified in specimens from the two hospitals that had tested positive for SC. Among the 24 SC positive PGHC specimens, marijuana (17 specimens), PCP (15) and cocaine (6) were the illegal drugs most likely found along with SC. Haloperidol (6) was also found, but was probably administered to these patients in the ED because of their agitated behavior. The 14 SC positive specimens from the UMMC patients were most likely to contain marijuana (10) and cocaine (4). Regardless of the specific drugs involved, multiple drugs were involved in most SC positive specimens, with 96 percent of the SC positive specimens from PGHC and 86 percent of those from UMMC containing at least one drug in addition to SC.

Correlates of testing positive for SC

We looked at whether the patient's self-report of recent SC use and/or having SC as a chief complaint was related to their testing positive for SC, marijuana, PCP, and/or another type of NPS (other than SC). Table 12 shows that in both groups, patients who self-reported SC use and/or had a chief complaint related to SC were significantly more likely to test positive for SC than persons who did not. However, SC was found in only 56 percent and 73 percent, respectively, of the patients in PGHC and UMMC who reported using it and/or had a chief complaint related to SC. It is also noteworthy that a small percentage (8% and 6%, respectively) of patients in both groups who did not report SC use and/or have a chief complaint related to SC did test positive for the drug. Patient reports of SC use and/or an SC-related chief complaint were not significantly related to testing positive for marijuana, PCP, or an NPS other than SC. Marijuana was detected in more than three-quarters of all patients regardless of whether they reported SC use and/or had a chief complaint related to SC. Patients in PGHC and UMMC who reported SC use but tested negative for the drug may have actually taken marijuana or another type of NPS. The PGHC patients may actually have also taken PCP.

Table 13 shows several possible correlates of testing positive for SC. Among all patients, 23 percent of those from PGHC and 20 percent from UMMC had tested positive for SC. As noted above, and also in Table 13, more than one half of the subset of patients who reported use of SC and/or had an SC-related chief complaint tested positive for the drug. Two of the correlates we looked at were associated with a 50 percent or higher likelihood of testing positive for SC. The two attributes were patients from PGHC aged 41 or older and patients from both hospitals where the treatment provider's certainty of SC use was a 5 (of 5). It is noteworthy that few of the PGHC patients (22%) and the UMMC patients (20%) had a treatment provider who had this high level of certainty regarding their SC use. We found that most of these patients had reported use of SC and/or indicated it was their chief complaint, likely leading to their provider's heightened level of certainty that they had used SC.

Table 8: Mean Age of Persons Positive for Specific Drugs, By Site

	Prince George's Hospital Center Mean Age *(n=106)*			UMMC, Midtown Campus Mean Age *(n=68)*^		
	(n)	$\bar{x}$	(SD)	(n)	$\bar{x}$	(SD)
All Patients	(106)	**31.2****	(10.6)	(68)	**37.2****	(12.8)
Positive by CDEWS Lab for:						
Marijuana	(73)	**29.4**	(9.7)	(41)	**33.1**	(11.2)
Any Benzodiazepine$^{\Delta}$	(12)	**26.9**	(7.9)	(23)	**41.5**	(11.9)
Any New Psychoactive Substance (NPS)	(23)	**32.2**	(13.2)	(21)	**39.1**	(13.8)
Any Non-Fentanyl Opioid$^{\Delta}$	(13)	**32.9**	(13.0)	(35)	**41.1**	(10.6)
Any Antidepressant$^{\Delta}$	(14)	**35.3**	(13.2)	(13)	**44.5**	(13.3)
PCP	(50)	**34.5**	(7.3)	(2)	-†	-†
Any Synthetic Cannabinoid	(24)	**35.8**	(11.2)	(14)	**38.1**	(12.0)
Cocaine	(23)	**36.7**	(12.7)	(32)	**39.0**	(11.2)
Any Fentanyl$^{\Delta}$	(4)	-†	-†	(19)	**41.5**	(10.2)
Methadone/EDDP	(1)	-†	-†	(13)	**38.3**	(10.2)

^One case was excluded due to missing demographic information.

†Not calculated due to low number of cases (n<10).

$^{\Delta}$It is not possible to definitively determine whether the presence of these drugs were due to illicit use or whether drugs were administered or prescribed by a physician; however, drug test results with evidence of the drug being administered to the patient by emergency department staff or evidence of patient taking the drug by prescription were counted as negative in this analysis.

**p<.01 by Independent Samples T-test.

Table 9: Number of Synthetic Cannabinoid Metabolites Detected in All Synthetic Cannabinoid Positive Specimens, By Site

	Prince George's Hospital Center (N=24)	**UMMC, Midtown Campus** (N=14)
# of Metabolites	*%*	*%*
1	50	64
2	29	36
3	13	0
4	8	0
Total	100	100

Metabolite Detected	**Prince George's Hospital Center** (N=24)	**UMMC, Midtown Campus** (N=14)
	%	*%*
MDMB-FUBINACA metabolite M1	71	100
MMB-FUBINACA	42	7
5F-AMB metabolite 7	29	0
FUB-PB-22 3-carboxyindole metabolite	0	21
5F-ADB metabolite 7	8	0
5F-PB-22 3-carboxyindole	8	0
JWH-073-N-COOH	8	0
PB-22 3-carboxyindole	4	0
BB-22 3-carboxyindole	4	0
AB-CHMINACA (metab 4)	4	0
ADB-FUBINACA (Parent)	0	7

Table 10: Other Drugs Detected in Specimens Positive* for Synthetic Cannabinoids at Prince George's Hospital Center

(N=24 synthetic cannabinoid positive specimens from Prince George's Hospital Center)^

	Opioids	Illicit Non-Opioid Drugs						Pharmaceutical Non-Opioid Drugs		
Specimen	Oxymorphone	Marijuana	PCP	Cocaine	mCPP†	Butylone	Dibutylone	Haloperidol$^{\Delta}$	Trazodone$^{\Delta\dagger}$	Total # of Drugs Detected‡
1			✓	✓	✓			✓	✓	5
2		✓	✓	✓		✓	✓			5
3		✓	✓			✓	✓			4
4	✓	✓	✓							3
5	✓	✓		✓						3
6	✓				✓				✓	3
7		✓	✓	✓						3
8		✓	✓					✓		3
9		✓				✓	✓			3
10		✓	✓					✓		3
11		✓	✓	✓						3
12		✓	✓					✓		3
13					✓			✓	✓	3
14			✓					✓		2
15			✓	✓						2
16			✓		✓					2
17		✓	✓							2
18		✓	✓							2
19		✓	✓							2
20		✓								1
21		✓								1
22		✓								1
23		✓								1
24										0
Total	3	17	15	6	4	3	3	6	3	60

*Includes specimens positive for any synthetic cannabinoid compound on the testing panel. See Table C-2 in Appendix C for full testing panel. Synthetic cannabinoids compounds detected: 5F-PB-22 3-carboxyindole, AB-CHMINACA (metab 4), BB-22 3-carboxyindole, JWH-073-N-COOH, PB-22 3-carboxyindole, 5F-ADB metabolite 7, 5F-AMB metabolite 7, MDMB-FUBINACA metabolite M1, and MMB-FUBINACA.

^Includes drugs detected in at least 10% of specimens. Drugs detected in under 10% included: Clonazepam/7-Aminoclonazepam, Codeine, Cyclobenzaprine, Dextromethorphan, Flunitrazepam, Furanylfentanyl, Hydrocodone, Hydromorphone, Methamphetamine, Morphine, Naloxone, Oxycodone, Paroxetine, Promethazine, and Tramadol.

†Trazodone is an antidepressant whose major active metabolite is mCPP. It is not possible to definitively determine whether the presence of mCPP was due to Trazodone use or whether mCPP was taken on its own.

$^{\Delta}$It is not possible to definitively determine whether the presence of these drugs were due to illicit use or whether drugs were administered or prescribed by a physician; however, drug test results with evidence of the drug being administered to the patient by emergency department staff or evidence of patient taking the drug by prescription were counted as negative in this analysis.

‡Two or more of the drugs may have been detected as a result of taking one substance.

Table 11: Other Drugs Detected in Specimens Positive* for Synthetic Cannabinoids at UMMC, Midtown Hospital

(N=14 synthetic cannabinoid positive specimens from UMMC, Midtown Hospital)^

	Opioids	Illicit Non-Opioid Drugs					Pharmaceutical Non-Opioid Drugs			
Specimen	Morphine[Δ]	Marijuana	Cocaine	Butylone	Dibutylone	mCPP[†]	Cetirizine	Demoxepam	Haloperidol[Δ]	Total # of Drugs Detected[‡]
1			✓	✓	✓		✓			4
2	✓	✓	✓				✓			4
3		✓		✓	✓					3
4	✓	✓	✓							3
5		✓		✓	✓					3
6		✓						✓	✓	3
7		✓	✓							2
8		✓							✓	2
9		✓				✓				2
10						✓		✓		2
11		✓								1
12		✓								1
13										0
14										0
Total	2	10	4	3	3	2	2	2	2	30

*Includes specimens positive for any synthetic cannabinoid compound on the testing panel. See Table C-2 in Appendix C for full testing panel. Synthetic cannabinoids compounds detected: ADB-FUBINACA (Parent), FUB-PB-22 3-carboxyindole metabolite, MDMB-FUBINACA metabolite M1, and MMB-FUBINACA.

^Includes drugs detected in at least 10% of specimens. Drugs detected in under 10% included: Alprazolam/α-Hydroxyalprazolam, Buprenorphine/Norbuprenorphine, Codeine, Desvenlafaxine/Desmethylvenlafaxine, Diazepam/Nordiazepam, Fentanyl/Norfentanyl, Fluoxetine, Lorazepam, Methadone/EDDP, Naloxone, Oxazepam, Quinidine/Quinine, Temazepam, Trazodone[†], and Venlafaxine.

[Δ]Note: It is not possible to definitively determine whether the presence of these drugs were due to illicit use or whether drugs were administered or prescribed by a physician; however, drug test results with evidence of the drug being administered to the patient by emergency department staff or evidence of patient taking the drug by prescription were counted as negative in this analysis.

[†]Trazodone is an antidepressant whose major active metabolite is mCPP. It is not possible to definitively determine whether the presence of mCPP was due to Trazodone use or whether mCPP was taken on its own.

[‡]Two or more of the drugs may have been detected as a result of taking one substance.

Table 12: Percentage of Patients that Tested Positive for Selected Drugs/Drug Categories, By Site and Patient Report/Chief Complaint of SC Use

	Prince George's Hospital Center (N=106)		UMMC, Midtown Campus (N=69)	
	Patient Report/Chief Complaint of SC Use‡ (N=32)	**No Report/Chief Complaint of SC Use‡** (N=74)	**Patient Report/Chief Complaint of SC Use‡** (N=15)	**No Report/Chief Complaint of SC Use‡** (N=54)
% Positive For				
1. Any Synthetic Cannabinoid	56%***	8%***	73%***	6%***
2. Marijuana	75	66	80	56
3. PCP	53	45	0	4
4. Any New Psychoactive Substance	31	18	40	30

‡Patient reported SC use defined as "patient reports recent synthetic cannabinoid use", "chief complaint related to synthetic cannabinoids", and/or "patient self-report or report by other representative of synthetic cannabinoid use in past 24 hours".
***p<.001 based on Chi Square or Fisher's Exact Test.

Table 13: Correlates of a Positive Test for Synthetic Cannabinoids (SC), By Site

	Prince George's Hospital Center (N=106)		UMMC, Midtown Campus (N=69)	
	Positive for SC (N)	%	Positive for SC (N)	%
All Patients	(106)	23%	(69)	20%
Gender				
Male	(81)	24	(60)	23
Female	(25)	20	(9)	0
Age				
≤ 25	(33)	12	(17)	18
26-35	(42)	21	(16)	19
36-40	(17)	24	(10)	30
41+	(14)	50	(25)	20
Patient Report/Chief Complaint of SC Use‡				
Yes	(32)	56***	(15)	73***
No	(74)	8***	(54)	6***
Treatment Provider's Certainty of SC Use				
1	(17)	0	(16)	0
2	(34)	9	(5)	-
3	(18)	17	(7)	-
4	(11)	9	(21)	14
5	(23)	70***	(12)	58***

9%*** 8%***

Note: Statistics not calculated on less than 10 cases.

‡Patient reported SC use defined as "patient reports recent synthetic cannabinoid use", "chief complaint related to synthetic cannabinoids", and/or "patient self-report or report by other representative of synthetic cannabinoid use in past 24 hours".

***p<.001 based on Chi Square or Fisher's Exact Test.

Study Limitations

The CDEWS model depends on re-testing a small number of specimens that have already been collected and tested by a local testing program. We do not know whether the small number of patients enrolled in this study are representative of all patients coming to these emergency departments for an SC-related health problem during the period of this study. The CDEWS results from criminal justice populations have been found to be internally consistent and often agree with other indicators of drug use in the studied populations (Wish et al., 2013, 2015). This CDEWS study was designed to learn more about the types of drugs recently used by patients appearing at the two emergency departments for an SC-related health problem and cannot provide precise prevalence estimates.

It should be noted that a number of patients were ineligible for the study (and consequently dropped from the sample) because a urine specimen was not collected for them. Urine specimens may not have been collected for a variety of reasons, including the patient being unconscious. It is not known whether the patients for whom a urine was unavailable differed from those for whom a urine specimen was collected.

Every effort was made to include in the CDEWS Laboratory test panel most of the currently available drugs likely to be misused. However, given the rapidly changing nature of new psychoactive substances, it is possible that some drugs may have been missed by the CDEWS testing panel. The continuously changing nature of the substances available make it difficult to develop urine tests for all of the new drugs as quickly as they are discovered. Even though we re-tested our specimens with a larger panel of SC metabolites, it is still possible that our results underdetected the SC that these patients might have used.

It is also possible that some SC analytes, particularly parent analytes, degraded during specimen holding, as the specimens were held briefly at room temperature prior to transfer to the hospital laboratory where they were placed in cold storage. Limited research suggests that there may be some fluctuation in SC analytes for urine specimens held at room temperature, while analytes in specimens held in cold storage have shown to be relatively stable over extended periods of time (Castaneto et al., 2014; Davies et al., 2016). This may have resulted in underestimates of SC use in the studied populations.

In addition, while we found that some specimens contained multiple drugs/metabolites, this does not necessarily mean that the user sought all of these drugs or was aware of the composition of the substance(s) ingested. Multiple drugs in a specimen may also simply reflect the byproducts produced from formulating, transporting, or taking the drug.

Summary and Conclusions

This study of patients appearing at the emergency department at Prince George's Hospital Center (PGHC, N=106) and at the UMMC, Midtown Emergency Department (N=69) for a presumed health consequence stemming from the use of a synthetic cannabinoid (SC) yielded a number of unexpected findings. Most surprisingly, only about one-fifth to one-quarter of specimens from each of the hospitals tested positive for SC, but they were likely to test positive for other drugs that reflected local drug use patterns. Given that patients were enrolled in the study due to a suspected SC overdose, our results underscore the challenges faced by physicians in identifying the drugs being used by patients presenting to the ED with an adverse drug-related event. Some of the findings are discussed below, grouped by theme.

The Profile of Patients Presenting with a Suspected SC Overdose is Varied and May Be Complicated by Patient Polydrug Use

While most participants from both hospitals sought care or were brought to the emergency department (ED) for a presumed health problem related to their use of SC, the demographics and clinical presentation of the patients from the two participating hospitals varied. UMMC patients were older, less agitated, and were more likely to report a chief complaint of an overdose or drug poisoning. The PGHC patients were more likely to be at the hospital because of an Emergency Petition or psychiatric event, and to exhibit bizarre or aggressive behavior. These differences may be explained in part by the variations found in the drugs being used by patients at the two hospitals. For example, almost half of the patients at PGHC in the study sample tested positive for PCP, a drug known to cause agitation. Few users of PCP were found at UMMC. In comparison, the patients in the study sample at UMMC were significantly more likely to be using fentanyl and non-fentanyl opioids, drugs that might precipitate calm or lethargy. The variation in these drug use patterns is not surprising given that PCP use is well documented in Prince George's County, the County in which PGHC is located, as well as in neighboring city of Washington, DC (Pretrial Services Agency for the District of Columbia, 1984-2017; Wish et al., 2009, 2017). Similarly, UMMC is located in Baltimore City, an area known to have a high prevalence of opioid use, particularly heroin (DHMH, 2017; Mars et al., 2017; Wish et al., 2009, 2017). In addition, there was significant variation in the SC metabolites detected in patients from each hospital, suggesting regional differences in the SC used.

When we examined the use of likely illicit drugs (drugs not likely to have been taken under a doctor's supervision) in both populations, the average specimen contained approximately two of the drugs or drug classes examined, but 33 percent of the specimens from patients at UMMC and 24 percent of those at PGHC contained three or more drugs/drug classes. For patients that had an SC positive urine specimen, multiple drugs were involved in most cases, with 96 percent of the SC positive specimens from PGHC and 86 percent of those from UMMC containing at least one drug in

addition to SC. It is not possible to know whether the multiple drugs detected were taken intentionally by the user or if the drugs they ingested contained multiple drugs without their knowledge. It is also possible that users were unaware that the substance they ingested contained SC, particularly given that SC was found in some specimens (9-13%) for persons who did not self-report SC use or have a chief complaint related to SC. It is also not possible to know whether the drugs identified were all used during the same episode or whether their presence was the result of previous recent use.

NPS were Detected in a Substantial Minority of Specimens at Both Hospital Sites

It is notable that an NPS other than SC was found in 22 percent of specimens from PGHC and 32 percent of specimens at UMMC. Dibutylone and butylone were most commonly found, with more dibutylone detected in patients at UMMC than PGHC. It is possible that the clinical presentation of persons experiencing an adverse event from using dibutylone and/or butylone may be similar to those experiencing an adverse event from SC. For example, adverse effects of butylone are reported to include nausea, vomiting, anxiety, excessive sweating, hyperthermia, tachycardia, hypertension and insomnia, symptoms which overlap with reported adverse effects of SC (Baselt, 2014, Gurney et al., 2014). Alternatively, it may be possible that the patient reported SC use but actually ingested another type of NPS. It may be important for physicians to consider use of other NPS when a patient presents to an ED with symptoms of an SC overdose.

Patients who test positive for Fentanyl are Likely to be Using Multiple Drugs

Our prior research (CESAR, 2017, 2017a; Wish et al., 2017) has shown that fentanyl positive specimens often test positive for multiple drugs. All 19 of the fentanyl positive specimens from patients at UMMC contained another drug, and 14 of the 19 specimens contained six or more drugs or metabolites. Morphine (a metabolite of heroin and codeine) was found in 95 percent of specimens, and cocaine (74%) and codeine (68%) were also commonly found in these fentanyl positive specimens. For any suspected users of fentanyl presenting to the ED, physicians should consider the high likelihood of polydrug use.

The Challenge of Detecting SC

The rapidly changing chemical structures of the illicit drugs marketed creates large problems for laboratories and researchers trying to detect the latest drugs. This is especially true for SC where manufacturers slightly modify a molecule so that the new drug is not included in the federal list of controlled drugs. One of the most important findings from the current study was how much our detection of SC metabolites was increased by the re-test results. In spite of our attempts to include in the laboratory's CDEWS test panel most of the widely known SC metabolites, our initial tests, which

could identify 26 SC metabolites, indicated that only one of the 175 specimens from patients in the two hospitals contained SC (5F-PB-22). Because prior CDEWS studies had detected multiple SC metabolites, including both new and older generation metabolites in the SC positive specimens, we believed that our tests were not likely to be missing SC use in these patients. However, this assumption proved to be incorrect. When the specimens were re-tested with a larger panel of 46 SC metabolites, we found SC in about one quarter of the specimens from each hospital. In addition, many of the SC positive specimens contained only a single metabolite, MDMB-FUBINACA metabolite M1, which had been newly added to the re-test panel. The formulation of SC with only a single metabolite or few metabolites was unexpected and will undoubtedly make detection of SC even more difficult. We conclude from our experiences that even the most up-to-date test panels will likely miss some of the newest SC metabolites and will underestimate their use. It is still possible that some of the patients we studied used a form of SC for which we could not test.

Correlates of testing positive for SC

More than one half of the patients who reported SC use and/or had a chief complaint related to it tested positive for SC. Only patients from PGHC aged 41 or higher and patients in both hospitals where the treatment provider's certainty of SC use was a 5 (of 5) had a similarly elevated likelihood of testing positive for SC. It is noteworthy that only a minority of the PGHC patients (22%) and the UMMC patients (20%) we studied had a treatment provider with this high a level of certainty that they had used SC. Nevertheless, this small minority of patients accounted for 70 percent of all SC positive cases from each of the hospitals.

If we had enrolled only patients for whom emergency department staff indicated they were extremely certain (a 5 out of 5 on our certainty scale) that the patient had used SC, most of that small subset of patients in our study would have tested positive for SC. The majority of patients whose treatment provider indicated the highest level of certainty that they had used SC either reported the use of SC or it was involved in their chief complaint. This finding supports the value of taking into account patients' reports of the drugs involved in their overdose. It should be noted, however, that few of the patients we studied reported use of the large variety of drugs they tested positive for.

The Special Challenges of Conducting a CDEWS Study in a Hospital Setting

This study was the first implementation of the CDEWS methodology in a hospital setting. Many of the challenges of conducting a CDEWS study in a hospital stemmed from our collection of additional clinical information on each subject, which may not be necessary for future CDEWS studies. To conduct this study, we collaborated with several emergency department physicians at each hospital to assist with recruitment and data collection. Some of the data collected relied on the subjective judgment of the physicians assisting with the study. It is possible that the physicians may

have differed in the manner in which these assessments were made. Collecting urine specimens from a hospital also presented challenges in locating a urine specimen from each patient. The interpretation of the CDEWS laboratory test results was also complicated by the possibility that some of the drugs detected had been administered in the ED or prescribed by a physician prior to the patient's hospital visit. Given this possibility, in cases where the patient tested positive for one or more drugs that were either administered or prescribed to the patient (based on their medical record), the patient's test result(s) for those drugs was counted as negative in all analyses.

Overall Study Implications

The results from this study clearly demonstrate the complexity of both detecting and treating patients reporting to the ED for an adverse drug-related event. Most hospitals and other public health settings lack the testing capacity we had to identify the drugs that had been recently used by their patients. Even within a setting that is able to test for many drugs, the panel will need to be periodically updated and will still be likely to underdetect certain types of drugs, especially NPS. Panel updates are time consuming for laboratories and may take 3-6 months to complete and validate, assuming that reference standards have been released for the compounds of interest. Many users will also not be able to accurately report the substance(s) which they have ingested because they are not aware of the true composition of the drugs they are taking. Both NPS and other types of drugs may be combined by dealers without the knowledge of the user. The best source of likely drug use for ED physicians may be the extant local epidemiologic research literature. The drugs we detected in the patients we studied, PCP in patients from Prince George's County and heroin and other opioids in patients from Baltimore City, have been shown by prior epidemiologic studies to be prevalent in these areas. Physician knowledge of local drug use patterns may therefore help them to anticipate the drugs that are most likely to be involved in their ED patients, even though patients have not specifically reported using them.

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