Title

The Psychoactive Surveillance Consortium and Analysis Network (PSCAN): the first year

Journal

Addiction, 115(2)

ISSN

0965-2140

Authors

Monte, Andrew A

Hopkinson, Andrew

Saben, Jessica

et al.

Publication Date

2020-02-01

DOI

10.1111/add.14808

Peer reviewed

HHS Public Access

Author manuscript

Addiction. Author manuscript; available in PMC 2021 February 01.

Published in final edited form as:

Addiction. 2020 February ; 115(2): 270–278. doi:10.1111/add.14808.

The Psychoactive Surveillance Consortium and Analysis Network (PSCAN): The First Year

Andrew A. Monte, MD, PhD[1,2], **Andrew Hopkinson, BS**[1], **Jessica Saben, PhD**[1], **Shelby Shelton, MPH**[1], **Stephen Thornton, MD**[3], **Aaron Schneir, MD**[4], **Adam Pomerleau, MD**[5], **Robert Hendrickson, MD**[6], **Ann M. Arens, MD**[7], **Jon B. Cole, MD**[7], **James Chenoweth, MD**[8], **Spencer Martin**[9], **Axel Adams, MS**[9], **Samuel D. Banister, PhD**[10,11], **Roy R. Gerona, PhD**[9]

[1]University of Colorado School of Medicine, Department of Emergency Medicine, Aurora, CO

[2]Rocky Mountain Poison & Drug Center, Denver Health and Hospital Authority, Denver, CO

[3]University of Kansas, Department of Emergency Medicine, Kansas City, KS

[4]University of California San Diego Health System, Division of Medical Toxicology, Department of Emergency Medicine, San Diego, CA, USA

[5]Department of Emergency Medicine, Emory University, Atlanta, GA

[6]Department of Emergency Medicine, Oregon Health and Science University, Portland, OR

[7]Department of Emergency Medicine, Hennepin Healthcare, Minneapolis, MN

[8]UC Davis Health, Sacramento, CA

[9]Clinical Toxicology and Environmental Biomonitoring Lab, University of California San Francisco, San Francisco, CA

[10]The School of Chemistry, The University of Sydney, Sydney, NSW, Australia

[11]The Lambert Initiative for Cannabinoid Therapeutics, The Brain and Mind Centre, The University of Sydney, Sydney, NSW, Australia

Abstract

Background and aims: The Psychoactive Surveillance Consortium and Analysis Network (PSCAN) is a national network of academic emergency departments (ED), analytic toxicologists, and pharmacologists that collects clinical data paired with biologic samples to identify and improve treatments of medical conditions arising from use of new psychoactive substances (NPS). The aim of this study was to gather clinical data with paired drug identification from NPS users that presented to EDs within PSCAN during its first year (2016–17).

Design: Observational study involving patient records and biological samples.

Setting: Seven academic emergency medical centers across the US.

Participants: ED patients (n=127) >18 years of age with possible NPS use who were identified and enrolled in PSCAN by clinical providers or research personnel.

Competing Interests: We have no competing interests to disclose

Measurements: Clinical signs, symptoms, and treatments were abstracted from the patients' health records. Biological samples were collected from leftover urine, serum, and whole blood. Biologic and drug samples, when available, were tested for drugs and drug metabolites via liquid chromatography-quadrupole time-of-flight mass spectrometry (LC-QTOF/MS).

Findings: Patients in which synthetic opioids were detected (n=9) showed higher rates of intubation (4/9), impaired mental status (4/9) and respiratory acidosis (5/9) compared with the rest of the cohort (9/118, p value <0.05). Patients in whom synthetic cannabinoid (SC) were found (n=27) had lower median diastolic blood pressures (70.5 mmHg vs 77 mmHg, p=0.0.046) compared with the rest of the cohort. In 64 cases of single drug ingestion, benzodiazepines were administered in 25 cases and considered effective by the treating physician in 21 (84%) cases.

Conclusions: During its first year of operation, the Psychoactive Surveillance Consortium and Analysis Network (PSCAN) captured clinical data on new classes of drugs paired with biologic samples over a large geographic area in the United States. Synthetic cannabinoids were the most common new psychoactive drug identified. Synthetic opioids were associated with a hih rate of intubation and respiratory acidosis.

Keywords

Novel; Psychoactive; Cannabinoids; Opioids; Stimulants; Synthetic

Introduction:

New psychoactive substances (NPS) are non-traditional drugs of abuse; they are often synthetic and designed by clandestine laboratories to have higher potency at targeted receptors than traditional drugs, such as cannabis and heroin. NPS are the fastest growing class of recreational drugs in the world.(1–3) These drugs are inherently difficult to detect due to the constantly changing chemical composition, even amongst drugs with the same street names.(4) The inability of traditional drug screens to detect NPS(5–7) and infrequent capture of biologic samples from drug users and abusers make it difficult for clinicians to match clinical syndromes with their causative agent. The class is complex. In fact, even the term NPS overly simplifies the complexity of these drugs.(8) Synthetic cannabinoids vary in potency and adverse effects, depending upon the compound used, and these drugs are often mixed with numerous intoxicating substances, including traditional drugs of abuse as is the case with heroin adulteration with fentalogues.(9) Moreover, failure to comprehensively test for all illicit drugs or pharmaceuticals may lead to false attribution of clinical effects to compounds identified on limited testing panels. Most epidemiologic studies that have examined these drugs focus on user reports, which may be inaccurate due to drug adulteration, drug substitution, and regional variation in local colloquial terminology. For instance, AMB-FUBINACA, a synthetic cannabinoid (SC) reported in numerous outbreaks of clinical illness associated with use, was called "AK-47" and "24 Karat Gold" by users in NY,(10) "Spice" in Germany,(11) "Mojo" in Louisiana,(12) and "Black Mamba" in Colorado.[3] "Black Mamba" is a more generic term for SCs in Denver, Colorado and these drugs have been identified to contain ADB-PINACA, MDMB-FUBINACA, ADB-FUBINACA, cocaine, and methamphetamine. The clinical syndromes between these

patients can vary significantly and subsequent identification of numerous drugs in user biologic samples demonstrates the unreliability of user reports.(4)

These factors complicate the ability of clinicians to provide therapeutic recommendations and prognosis in patients that are clinically ill from using these drugs. There are no universally accepted treatment strategies for these patients. Many treatment strategies are regionalized, such as ketamine use for acute out-of-hospital agitation,(13) which is frequently administered in the US Midwest but is infrequently used in other areas.(14) Since NPS compounds are often present in a community for a distinct time-period effectiveness and safety of these treatments may vary as the compounds transition in a region. Retrospective case series will not reflect this variability or the effectiveness and safety of their treatment. Thus, a prospective cohort study that identifies clinical signs and symptoms and pairs these syndromes with NPS analysis in biologic samples is necessary.

It has become clear that a geographically representative network, with codified definitions, can benefit from expansion. This allows for assessment of treatment effectiveness and safety by the treating physicians using standardized definitions of clinical signs and symptoms, similar to the National Poison Data System.(15) However, due to the failure of self-report or inability of the bedside clinician to accurately identify the causative compound, particularly given the lack of uniformity in naming synthetics and the variability in chemical composition across synthetics, the network must be able to gather biologic samples to identify and quantify the NPS exposure responsible. The proposed prospective surveillance can be used to identify trends in NPS abuse, detail regional spread of noxious compounds, and demonstrate trends in treatment effectiveness and safety. This need prompted the formation of the Psychoactive Surveillance Consortium and Analysis Network (PSCAN) in 2016. The objective of this manuscript is to describe the clinical data obtained from cases captured by PSCAN through 2017. A separate manuscript will outline the drug detection processes and the specific compounds detected in these patients.

Methods:

Consortium Constituents

PSCAN was established as a collaborative effort on July 1st, 2016. The consortium is composed of medical toxicologists that collect and document clinical findings in cases at their local site and analytical toxicologists that perform NPS analysis. Data are obtained through consultation and communication with clinicians caring for the patients seen at each of the consortium sites. This allows for broad capture of cases by front line providers resulting in data collection from the full range of mild to severe clinical illness. This design differs from case-series to date, which are biased toward the most severe presentations, while patients that are transiently intoxicated and rapidly discharged from emergency departments are not represented.(16) The University of Colorado Anschutz Medical Center acts as the clinical coordination center while the University of California San Francisco operates as the drug detection laboratory for the consortium. All sites obtained local institutional review board approval for de-identified collection of clinical data from acute cases of NPS exposure paired with collection of biologic samples. The protocol allows for waiver of consent to collect leftover biologic samples in de-identified patients. See Figure 1 for sites.

The University of California San Francisco, the University of Colorado, the University of Kansas and the Oregon Health and Science University were the original members of the network. Additional sites joined through 2016 and 2017. IRB applications were shared and submitted by individual site liaisons and training on the data collection form was performed by AA prior data collection. See Figure 2 for the timing of site on-boarding.

Patient Recruitment

Patients with potential NPS exposure are identified by clinical providers upon arrival to a PSCAN associated ED. ED providers are given very general instructions to target any patient for which there is a suspicion of a new psychoactive substance use. This may include designer drugs, such as synthetic cannabinoids, drugs used in new ways, such as injecting of a drug that is not typically injected, or patients that report traditional drug use but have unexpected or more severe reactions. Eligible patients are referred to the site investigator or study coordinator who then determines patient eligibility. Research staff obtain verbal consent from patients when sober and able to consent.

Data Collection Tool

A clinical reporting form, housed in the University of California-San Francisco instance of REDCap,(17) is used to capture clinical signs and symptoms. All data are deidentified and are entered into the data collection form (see Appendix 1) by the local site investigator or site coordinator. This form has the following domains: case summary, patient encounter presentation, subsequent patient encounter, lab results, treatment, and NPS test results. The “case summary” domain identifies the facility from which the sample was sent, the drugs the patient reported taking, and the clinical outcome. The “patient encounter at presentation” domain captures basic demographics, the presentation vital signs, the most severe vital sign derangements, and the physical exam. The “subsequent encounter” form summarizes illness progression and duration. Laboratory values focused on organ dysfunction; urine toxicology screening results are also documented in the laboratory data domain. We document all treatments, their effectiveness as determined by the ED provider, and any adverse drug events captured during the acute phase of clinical illness. Treatment effectiveness during this pilot phase was determined by the bedside clinician as a global assessment following drug administration. Finally, the NPS testing domain includes the identified compounds from biologic samples collected from these patients. Each patient is given a unique study ID so that data can be paired with the results of biologic sample testing.

Sample preparation and shipping

The initial samples at the time of presentation are placed in 4°C refrigerators. We collect leftover urine and whole blood from initial clinical sample collection for serum separation. Whole blood samples are centrifuged at 3000 rpm for 10 minutes, aliquoted into cellular and serum fractions, and frozen at −80°C. Samples are shipped on dry ice to the University of California San Francisco Clinical Toxicology and Environmental Biology Laboratory for analysis.

Drug identification and quantification

Serum and urine samples are analyzed using liquid chromatography-quadrupole time-of-flight mass spectrometry (LC-QTOF/MS, Agilent LC1260- QTOF/MS6550, Agilent Technologies, Santa Cruz, CA). For qualitative screening, non-targeted data acquisition was performed during the sample run followed by targeted data analysis using a reference database. The targeted drug screen database includes 768 drugs for which the CTEB Lab has available reference standards. This library includes 466 NPS, 184 traditional illicit drugs, and 118 prescription drugs. Of the 466 NPS, 116 are prophetic cannabinoids synthesized by our group, majority of which are neither commercially available nor disclosed in the literature. For suspect screening we compiled suspect drug screen databases for four general classes of NPS; stimulants (492 compounds), hallucinogens (210 compounds), sedatives-opioids and benzodiazepines (205 compounds) and cannabinoids (800 compounds).

Quantification of each confirmed drug was done using a 10-point calibration curve by isotope dilution using deuterated internal standards. The details of the LC-QTOF/MS method used were published previously.[12] Details of the compounds identified during drug testing results will be presented in another manuscript and not discussed in detail in this clinical manuscript.

Data sharing

All data are shared openly between PSCAN members. During periodic conference calls, we discuss toxidrome trends, drug identification results, and singular cases. During these calls, publication plans and authorship are agreed upon by consortium members. Local outbreaks of clinical illness, as defined by an atypical increase in visits to a consortium site, will be rapidly communicated to the local Departments of Public Health in an attempt to mitigate morbidity and mortality. All data remains de-identified and no personal health information is stored on any patient.

Clinical Signs and Symptoms Analysis:

Clinical data were extracted from individual case reports into a single database. Cases were sorted into specific NPS class groups based on the substances detected using LC-QTOF/MS. Drugs are grouped into chemical classes for drug detection results and pharmacologic classes for clinical analyses. Thus, in this clinical report we have grouped all SCs, opioids, stimulants (including cathinones, amphetamines, piperazines, and other stimulants), benzodiazepines, and hallucinogens.

Statistical Analysis:

Summary statistics were generated for demographic variables. Patients in which multiple drug classes were detected were excluded for clinical symptom statistics were only calculated in patients in which only a single drug class was identified to minimize the effects of polydrug exposure. Medians and interquartile ranges were calculated for all clinical elements captured. Differences in clinical signs and symptoms between those testing positive for an NPS and those testing negative were tested using the Mann-Whitney U test (continuous variables) or Chi-squared test (binary variables). Differences of the medians and 95% confidence intervals were calculated for clinical symptoms. For each NPS class, we

provide descriptive statistics on treatment: frequencies of each treatment, and frequencies of apparent treatment effectiveness, based on local investigator's judgement.

Results

Case enrollment and demographics

PSCAN captured 127 cases in patients 18 years and older with paired urine and/or blood samples over the initial pilot period. This number reflects staggered operationalization of sites (See Figure 2). Compound identities are listed in Appendix 2. Our cohort was predominantly male with a median age of 27 years old (Table 1). Stimulants and SCs were the most often detected class of NPS (Table 1). Four patients, in which multiple drugs classes were detected, were excluded from individual NPS class groups, to avoid confounding, though these patients were included in the comparator groups.

Clinical Syndromes

The most common physical exam findings found in the overall cohort were agitation, delirium and decreased mental status. Physical exam findings differed between each NPS class with synthetic opioids providing the most defined toxidrome. Patients with confirmed synthetic opioids in their biologic samples had the highest proportion of intubation (n=4, 44%), and decreased mental status (n=4, 44%). Presentation respiratory rates (RR) did not differ in the opioid pharmacologic group, likely due to the high number of patients intubated leading to a higher median RR than expected. However, these patients did display decreased blood pH likely caused by acute respiratory distress. Vital signs varied between NPS classes and there were few clinically relevant differences. Compared to the non-synthetic cannabinoid users, the SC cohort displayed decreased diastolic blood pressures at presentation. There were no other significant differences in vital signs between the other NPS classes.

Hospital Testing

The synthetic opioid cohort, while only having 9 patients, had significantly decreased blood pH (Table 3, p=0.046), serum calcium concentration (Table 3, p=0.046) and blood urea nitrogen (p=0.047) when compared to the remaining cohort. This same population also showed significant increases in $p0_2$ (Table 3, p=0.046) and QTc interval, determined by Bazett's formula (Table 3, 0.046) when compared to the remaining patient population. However, the differences observed in serum calcium concentration and blood urea nitrogen were within the normal range and not clinically relevant. Clinical immunoassay drug screens were positive for traditional drugs of abuse (cocaine, heroin, cannabis, benzodiazepines, amphetamines, barbiturates, or phencyclidine) in 72 (57%) patients.

Treatments

The most common treatment administered in all pharmacologic classes were benzodiazepines. Each NPS class received benzodiazepine treatment at comparable rates (Table 4). Benzodiazepines and antipsychotics were observed to have 100 % effectiveness by treating physicians in the SC group. Benzodiazepines were effective 70% of the time in the 10 patients with confirmed stimulant exposure. Interestingly, four patients with

confirmed synthetic opioid exposures received benzodiazepines for agitation after naloxone treatment and 75% of these were effective at providing the desired sedation. Antipsychotics were effective 57% of the time in 7 patients with confirmed stimulant exposure. Not surprisingly, patients in which SCs or stimulants were detected did not respond to naloxone. Naloxone was effective in four of the five cases in which it was administered in patients with confirmed synthetic opioids intoxication. A low amount of fentanyl, was detected in the one patient that did not respond to naloxone 2 mg intramuscularly. In this case, emergency medical services administered both midazolam and naloxone due to alternating sedation/confusion and agitation.

Clinical Outcomes

There was a single death reported over the study period. This patient presented with possible cocaine and phencyclidine intoxication. The patient stated that “It doesn’t matter, I’ll be dead soon anyway” before becoming unresponsive and experiencing a cardiac arrest. Patient had return of spontaneous circulation following 45 minutes of CPR but expired shortly after. A clinical urine toxicology screen was performed and returned positive results for benzodiazepines, cocaine and PCP. Additionally, we were able to detect the presence of fentanyl and 6-allyl-6-nor-LSD (AL-LAD; an LSD analogue) using LC-QTOF/MS.

Thirty-eight (30%) patients were discharged directly from the ED, 22 (17%) were admitted to observation units, 23 (18%) were admitted to the hospital and 38 (30%) were admitted to intensive care units. Significant differences were observed in patient disposition when the SC cohort was compared to the rest of the patient population. Patients in the SC cohort were more likely to be discharged directly from the emergency department or admitted for observation. These patients were also significantly less likely to expire or be admitted to a hospital floor or ICU. There was no significant difference in patient disposition overserved when the synthetic opioid and synthetic stimulant cohorts were compared to the rest of the cohort.

Discussion:

PSCAN is the first consortium able to capture clinical data paired with biologic samples over a large geographic area in the United States. By pairing clinical data with biological samples, we can identify discrete populations of drug class users and better define the toxidromes associated with individual novel and synthetic substances of abuse. We hope to move away from the term “NPS” as we find it imprecise, given the complexity of each individual compound and the common occurrence of poly-drug ingestion. Designer drug classes and even drugs within the same class, have different clinical effects due to variable receptor interactions and variable potencies at these receptors. However, as expected, our data indicate that individuals using synthetic opioids have increased prevalence of respiratory distress requiring intubation and mechanical ventilation. This finding is corroborated by the increased respiratory acidosis and pO_2 that were also observed in the opioid cohort. We were able to observe significantly decreased diastolic blood pressures in the SC cohort. However, other vital signs of the SC cohort did not significantly differ from the rest of the population. As PSCAN matures and collects more cases, we may have

increased power to further define the SC toxidrome by both pharmacologic class (stimulant and opioid, as presented here, for instance) and drug class (cathinones and piperizines, for instance). We believe that individual compounds may have more consistent toxidromes, if doses are similar, than what is currently observed across the entire SC class. Our inability to detect significant differences in clinical manifestations or vital sign abnormalities between the synthetic stimulant cohort and the rest of the population also indicates either a need for more cases to increase power or overlap in the associated toxidromes. While this represents a large cohort of patients intoxicated from designer drugs, this report is based upon a relatively small number of cases overall, and the subgroups are subsequently smaller. PSCAN may serve to more precisely define these toxidromes by virtue of collecting more cases than other groups with more complete toxicologic testing of blood and urine samples to confirm exposure, though these initial observations are inherently underpowered.

Synthetic cannabinoids are the most common drug identified through PSCAN. In this cohort, SCs led to less severe clinical outcomes, as demonstrated by a lower ICU and hospital admission rates, compared to other drug classes. This is contrary to other studies that have focused on critically ill patients with SC abuse.(16, 18, 19) As the numbers of cases involving other NPS products increase through PSCAN, we will likely see a more representative spectrum of clinical illness, as we have demonstrated with SCs. Our treatment data demonstrate that the most commonly used therapies are benzodiazepines followed by antipsychotics. This initial dataset suggests that benzodiazepines, antipsychotics, and ketamine have effectiveness at controlling agitation and delirium. However, benzodiazepines had the highest effectiveness, as determined by the treating clinician. We believe that collection of additional cases may allow for more granular analysis of treatment effectiveness between NPS drug classes. These preliminary data regarding the effectiveness of treatments for agitation and delirium should be interpreted with caution, as effectiveness was measured by the treating physician’s global satisfaction with the drug and not by a more objective measure such as a change in agitation score(20) or proportion of patients adequately sedated after injection.(21) Nevertheless, the perceived effectiveness of benzodiazepines is consistent with recently published data demonstrating midazolam was superior to the injectable antipsychotics olanzapine, ziprasidone, and haloperidol in terms of the proportion of patients adequately sedated 15 minutes after injection.(22) We hope future work will help us elucidate if specific drugs (or combinations) are more effective than others for agitated delirium from various novel psychoactive substances. Our hope is PSCAN will allow for us to gather high quality, prospective data to determine the optimal therapeutic choices for rapid, effective, safe sedation. There were no adverse drug events though these events are inherently uncommon and may be affected by individual patient factors, such as genetic polymorphism. This cohort may eventually allow for examination of these associations.

This work has several important limitations. PSCAN still only collects a convenience sample of NPS users presenting to a small group of academic medical centers and it therefore may not be representative of community NPS users. Additionally, effects arising from differences between sites, i.e. clustered-effects, may falsely raise the significance of our findings across the dataset. As this dataset matures, we will employ a regression models for clustered data to account for regional variability between sites. While powerful in our untargeted drug

detection methodology we still may have false negatives when we are not able to characterize an unidentified MS peak or if there is overlap between numerous peaks. Treatment effectiveness was determined by the bedside clinician during this pilot phase leading to subjective results. Polydrug ingestions result in mixed toxidromes which is why we have analyzed clinical signs and symptoms in single drug class cases only. We hope to integrate quantitative results from the biologic testing to determine the predominant toxidrome in future analyses of these data.

Pairing of clinical symptoms, clinical outcomes, and biological samples through PSCAN allows determination of specific toxidromes associated with these new substances. A better understanding of the clinical toxidromes associated with NPS use allows providers to make more appropriate treatment decisions resulting in better outcomes for patients. PSCAN has the largest and most expansive panel of NPS allowing for un-paralleled detection power.

Future Directions

We have added sites in the Southern and Northeastern regions in order to bolster sample capture and increase regional diversity in our cohort. We anticipate adding additional sites periodically as funding allows. We have moved toward a centralized IRB system, with peripheral sites ceding to the Colorado Multiple Institutional Review Board, in order to ensure regulatory consistency and decreased burden on consortium sites. Additionally, we expect expansion to enroll patients less than 18 years of age broadly, as some sites are already enrolling patients of all ages. Additionally, we have formalized the definitions of treatment effectiveness with validated tools based upon the symptom treated to more objectively characterize treatment effects. PSCAN has the capacity to collect serial biologic samples allowing for pharmacokinetic and pharmacodynamic characterization of NPS. We hope to examine genomic and metabolomic markers of drug toxicity to further examine the pathophysiology of illness associated with the increasingly complex NPS pharmacology.

In summary, PSCAN represents a flexible surveillance network with unique drug detection capabilities. Additional case capture will improve the ability to associate clinical syndromes with specific NPS classes. This consortium may allow for earlier prediction of regional NPS spread

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments/Funding:

The contents of this work are the sole responsibility of the authors and do not necessarily represents the views of the National Institutes of Health (NIH). Dr. Monte received support from NIH 1 K23 GM110516, NIH CTSI UL1 TR001082, and the Department of Defense #FA8650-18-2-6833 to support this work.

References

1. Cottencin O, Rolland B, Karila L. New designer drugs (synthetic cannabinoids and synthetic cathinones): review of literature. Curr Pharm Des. 2013.

2. Johnston L, O'Malley P, Bachman J, Schulenber J. Monitoring the Future national results on adolescent drug use: Overview of key findings, 2012. Institute for Social Research 2013(Th University of Michigan):83pp.

3. Arens AM, Olives TD, Simpson NS, Laes JR, Anderson DL, Bangh SA, et al. An outbreak of synthetic cannabinoid exposures reported to a regional poison center: "K2" identified as 5F-ADB. Clin Toxicol (Phila). 2018:1–2.

4. Brandehoff N, Adams A, McDaniel K, Banister SD, Gerona R, Monte AA. Synthetic cannabinoid "Black Mamba" infidelity in patients presenting for emergency stabilization in Colorado: a P SCAN Cohort. Clin Toxicol (Phila). 2017:1–6.

5. Begeman A, Franssen EJF. Lack of Detection of New Amphetamine-Like Drugs Using Conventional Urinary Immunoassays. Ther Drug Monit. 2018;40(1):135–9. [PubMed: 29194289]

6. Pettersson Bergstrand M, Helander A, Hansson T, Beck O. Detectability of designer benzodiazepines in CEDIA, EMIT II Plus, HEIA, and KIMS II immunochemical screening assays. Drug Test Anal. 2017;9(4):640–5. [PubMed: 27366870]

7. Regester LE, Chmiel JD, Holler JM, Vorce SP, Levine B, Bosy TZ. Determination of designer drug cross-reactivity on five commercial immunoassay screening kits. J Anal Toxicol. 2015;39(2):144–51. [PubMed: 25492523]

8. Potter GR, Chatwin C. Not particularly special: critiquing 'NPS' as a category of drugs. Drugs: Education, Prevention and Policy. 2018;25(4):329–36.

9. O'Donnell JK, Halpin J, Mattson CL, Goldberger BA, Gladden RM. Deaths Involving Fentanyl, Fentanyl Analogs, and U-47700 – 10 States, July-December 2016. MMWR Morb Mortal Wkly Rep. 2017;66(43):1197–202. [PubMed: 29095804]

10. Adams AJ, Banister SD, Irizarry L, Trecki J, Schwartz M, Gerona R. "Zombie" Outbreak Caused by the Synthetic Cannabinoid AMB-FUBINACA in New York. N Engl J Med. 2017;376(3):235–42. [PubMed: 27973993]

11. Lam RPK, Tang MHY, Leung SC, Chong YK, Tsui MSH, Mak TWL. Supraventricular tachycardia and acute confusion following ingestion of e-cigarette fluid containing AB-FUBINACA and ADB-FUBINACA: a case report with quantitative analysis of serum drug concentrations. Clin Toxicol (Phila). 2017;55(7):662–7. [PubMed: 28393558]

12. Shanks KG, Clark W, Behonick G. Death Associated With the Use of the Synthetic Cannabinoid ADB-FUBINACA. J Anal Toxicol. 2016;40(3):236–9. [PubMed: 26755539]

13. Cole JB, Klein LR, Nystrom PC, Moore JC, Driver BE, Fryza BJ, et al. A prospective study of ketamine as primary therapy for prehospital profound agitation. Am J Emerg Med. 2017.

14. Buckland DM, Crowe RP, Cash RE, Gondek S, Maluso P, Sirajuddin S, et al. Ketamine in the Prehospital Environment: A National Survey of Paramedics in the United States. Prehosp Disaster Med. 2018;33(1):23–8. [PubMed: 29265995]

15. Gummin DD, Mowry JB, Spyker DA, Brooks DE, Osterthaler KM, Banner W. 2017 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 35th Annual Report. Clin Toxicol (Phila). 2018:1–203.

16. Monte AA, Calello DP, Gerona RR, Hamad E, Campleman SL, Brent J, et al. Characteristics and Treatment of Patients with Clinical Illness Due to Synthetic Cannabinoid Inhalation Reported by Medical Toxicologists: A ToxIC Database Study. J Med Toxicol. 2017;13(2):146–52. [PubMed: 28397128]

17. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377–81. [PubMed: 18929686]

18. 3 dead, more than 100 with severe bleeding from synthetic pot: Illinois health officials [press release]. abcnews2018.

19. Monte AA, Bronstein AC, Cao DJ, Heard KJ, Hoppe JA, Hoyte CO, et al. An outbreak of exposure to a novel synthetic cannabinoid. N Engl J Med. 2014;370(4):389–90. [PubMed: 24450915]

20. Calver LA, Stokes B, Isbister GK. Sedation assessment tool to score acute behavioural disturbance in the emergency department. Emerg Med Australas. 2011;23(6):732–40. [PubMed: 22151672]

21. Cole JB, Moore JC, Dolan BJ, O'Brien-Lambert A, Fryza BJ, Miner JR, et al. A Prospective Observational Study of Patients Receiving Intravenous and Intramuscular Olanzapine in the Emergency Department. Ann Emerg Med. 2017;69(3):327–36 e2. [PubMed: 27823873]

22. Klein LR, Driver BE, Miner JR, Martel ML, Hessel M, Collins JD, et al. Intramuscular Midazolam, Olanzapine, Ziprasidone, or Haloperidol for Treating Acute Agitation in the Emergency Department. Ann Emerg Med. 2018;72(4):374–85. [PubMed: 29885904]

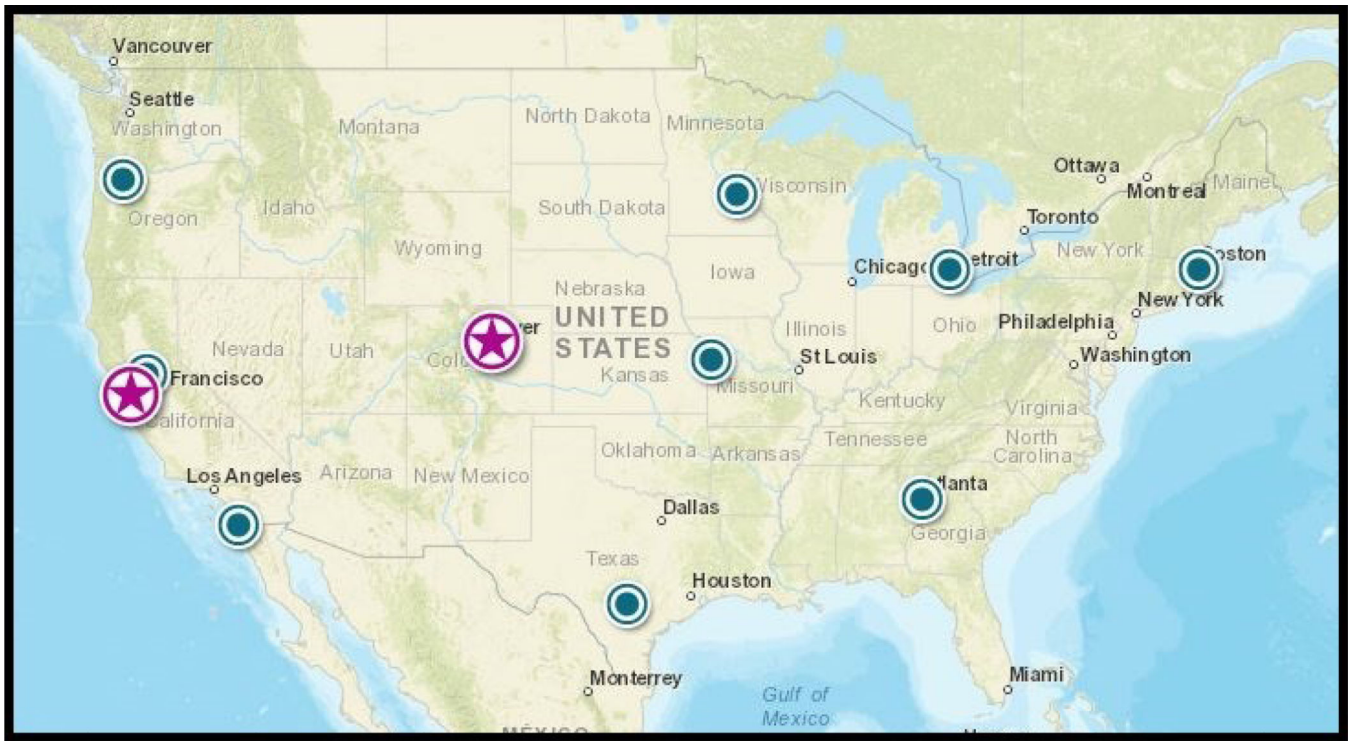

Figure 1.

PSCAN Sites. Stars represent University of California San Francisco, the drug detection analytic laboratory and the University of Colorado, the Clinical Coordinating Center for PSCAN. Figure produced in National Geographic Map Maker. https://mapmaker.nationalgeographic.org/

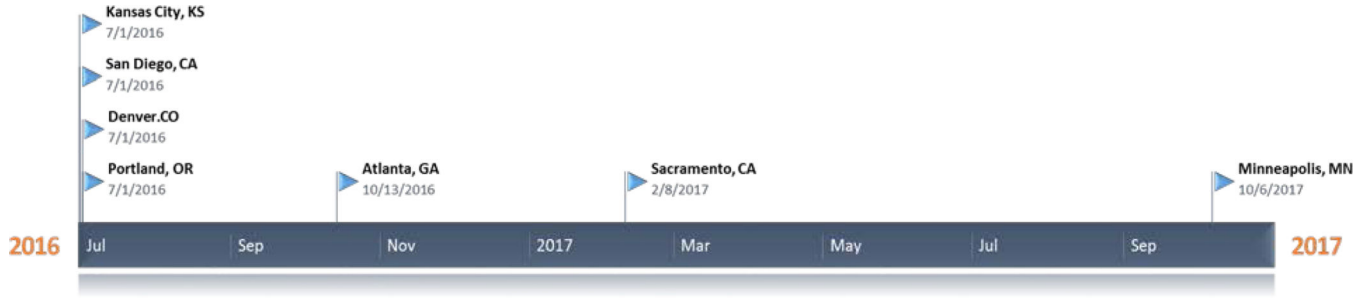

Figure 2.
Timeline of consortium on-boarding and sample collection.

Table 1.

Demographics, Location of Exposure, and Class of Drug Exposure of PSCAN Patients

Demographic Variable	Summary Statistic
Median Age (IQR)	27 (15.2%)
Male Gender, n (%)	98 (77.2%)
Number of Cases per Site, n (%)	
Denver, CO	44 (34.6%)
Kansas City, KS	40 (31.5%)
San Diego, CA	13 (10.2%)
Atlanta, GA	12 (9.4%)
Portland, OR	10 (7.9%)
Minneapolis, MN	6 (4.7%)
Sacramento, CA	2 (1.6%)
NPS Pharmacological Classes, n (%)	
Stimulant	27 (21.3%)
Synthetic Cannabinoid	27 (21.3%)
Synthetic Opioid	9 (7.1%)
Hallucinogen	1 (0.8%)
Benzodiazepine	1 (0.8%)

Table 2:

Vital signs at hospital presentation stratified by patients cohorts with discrete NPS class exposure.*

	Positive Cohort		Negative Cohort				
Synthetic Cannabinoid (n=27)	**Median**	**IQR**	**Median**	**IQR**	**p-Value**	**Difference in medians (IQR)**	**Mean difference of medians (95% CI)**
Heart Rate	93.5	81.25 – 114.25	101	85 – 130	0.220		
Systolic Blood Pressure	130.5	111.5 – 142.25	131	118.75 – 144.25	0.473	0.5 (−1.5, 4.0)	0.34 (0.21, 0.46)
Diastolic Blood Pressure	70.5	58 – 83.25	77	66 – 89.25	0.046	−0.002 (−3.11, 3.29)	0.04 (−0.09, 0.18)
Respiratory Rate	16.5	16 – 18.5	18	16 – 22	0.099	00 (−1.0, 0.0)	−0.28 (−0.31, −0.26)
Temperature	36.6	84.75 – 121.5	36.7	85 – 130	0.958	0.0 (−0.1, 0.05)	−0.003 (−0.003, 0.001)
Stimulant (Including amphetamines, cathinones, piperazine, etc.) (n=27)							
Heart Rate	94	83 – 121	101	85 – 121	0.535	0.0 (−7, 3.5)	−0.7 (−0.89, −0.52)
Systolic Blood Pressure	136	118.5 – 146	131	116 – 143	0.525	0.5 (−1.5, 4.0)_	0.21 (0.09, 0.34)
Diastolic Blood Pressure	80	66.5 – 89.5	75	64 – 86	0.412	−0.002 (−3.15, 3.15)	−0.002 (−0.13, 0.13)
Respiratory Rate	18	17 – 20	18	16 – 20	0.279	0.0 (−1.0, 0.0)	−0.29 (−0.32, −0.27)
Temperature	36.9	116 – 143.25	36.6	85 – 130	0.189	0.0 (−0.1, 0.1)	−0.001 (−0.001, −0.005)
Synthetic opioid (n=9)							
Heart Rate	101	88 – 103	100	83.75 – 123.75	0.828	0.0 (−8.0, 4.5)	−0.14 (−0.47, 0.19)
Systolic Blood Pressure	131	129 – 135	131	115.5 – 143.25	0.942	0.5 (−4.0, 5.0)	0.05 (−0.18, 0.29)
Diastolic Blood Pressure	82	77 – 85	75	64.75 – 87	0.303	0.0 (−5.0, 6.0)	0.43 (0.24, 0.63)
Respiratory Rate	20	15 – 20	18	16 – 20	0.958	−0.5 (−1.5, 0.5)	−0.16 (−0.21, −0.12)
Temperature	36.5	65 – 87	36.7	85 – 130	0.312	0.0 (−0.1, 0.1)	−0.002 (−0.008, 0.004)

* Sample restricted to individuals who in which only a single drug class was identified, to minimize the effects of polydrug exposure

Table 3:

Clinical testing results for the synthetic opioid cohort. Values are medians with interquartile ranges.*

	Synthetic Opioid (n=9)		Non-Opioid (n=118)		
Hospital Testing	**Median**	**Interquartile Range**	**Median**	**Interquartile Range**	**p-Value**
Serum Electrolytes					
Sodium	140.50	137.75 – 142.25	140.00	137 – 142	0.854
Calcium	8.90	8.1 – 9.25	9.40	8.9 – 9.85	0.046
Chloride	103.00	101 – 105.75	104.00	101 – 107	0.691
Potassium	3.95	3.35 – 4.1	3.60	3.4 – 3.9	0.476
Bicarbonate	21.00	18.5 – 26.5	22.00	19 – 24.75	0.85
Magnesium	2.30	2.225 – 2.325	2.10	1.9 – 2.3	0.368
Liver Function					
Alanine Aminotransferase	32.00	21 – 42.5	25.00	17 – 47.5	0.93
Aspartate Aminotransferase	41.00	25 – 53	29.00	21 – 50.5	0.72
Blood Gases					
pO_2 (mmHg)	157.00	70 – 270	57.00	39 – 87	0.038
pCO_2 (mmHg)	47.00	46 – 73	44.00	39 – 54	0.393
pH	7.22	7.19 – 7.26	7.30	7.2475 – 7.3525	0.046
Metabolic Panel					
Creatinine	1.01	0.985 – 1.0825	0.91	0.795 – 1.175	0.311
Glucose	126.00	111 – 153.75	107.00	92.75 – 128	0.251
Lactate	5.30	3.95 – 6.3	4.05	1.475 – 5.4275	0.347
Blood Urea Nitrogen	9.50	7.75 – 14.5	15.00	11 – 19	0.047
Cardiac Function					
Creatine Kinase	1726.50	360.25 – 4662	537.00	154 – 1916	0.526
EKG					
QRS Interval	94.00	79 – 97	88.00	83 – 96	0.833
QTc Interval	473.00	452 – 476.5	444.00	425 – 463.5	0.046

*Sample restricted to individuals who in which only a single drug class was identified, to minimize the effects of polydrug exposure

Table 4.

Treatments administered and associated effectiveness stratified by confirmed drug exposure classes

Drug Class	Benzodiazepine treatment (n that were effective)	Antipsychotic treatment (n that were effective)	Both benzodiazepine and antipsychotic treatment (n that were effective)	Naloxone treatment (n that were effective)
Synthetic cannabinoid Only (n=27)	11 (11)	5 (5)	4 (4)	2 (0)
Stimulant Only (n=27)	10 (7)	7 (4)	4 (3)	4 (0)
Synthetic opioid Only (n=9)	4 (3)	0 (0)	0 (0)	5 (4)