DOTS *Bulletin*

A Pilot Study of the
National Drug Early Warning System (NDEWS)
University of Maryland, College Park

Drug Outbreak Testing Service

June 2018 ◊ Issue 2

First DOTS Study Finds Fentanyl and Polydrug Use in Patients Seen During Opioid Overdose Spike in Baltimore – Higher Doses of Naloxone May Be Needed

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Submitting Site

Emergency Department of the University of Maryland: Midtown Campus

THE DRUG OUTBREAK TESTING SERVICE (DOTS) PILOT STUDY

DOTS tests up to 20 urine specimens for 240 drugs, without cost to the submitting site, to help identify emerging drugs for epidemiologic purposes.

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Background

An increased number of patients presenting with apparent opioid overdose in May 2017 prompted the Baltimore City Health Department to issue a city-wide warning for emergency departments, police, and emergency medical services. These patients required more naloxone than usual and were violent upon reviving. For safety, some providers had to then sedate these patients. Although it is common for some patients to be angry and/or experience withdrawal after being given naloxone, patients are rarely agitated to the point of needing sedation. The presentation in these cases led some officials to believe this was due to the increasing prevalence of fentanyl and synthetic cannabinoid (SC) use. In addition, the results of a prior study[1] conducted in this Emergency Department (ED) suggest that some patients may be using synthetic cathinones, commonly known as "bath salts." DOTS was asked to analyze the urines of patients treated for apparent opioid overdose over a two-day period to determine the substances that were involved in these cases.

Methods

Urine samples are often taken as a part of a patient's regular care in the ED. Excess urine was available for 8 of the 12 patients seen for an apparent opioid overdose during the two-day study period, May 26 and 27, 2017. These eight specimens were sent to DOTS for testing to look for drugs beyond those that could be tested for in this ED. Midtown's onsite laboratory urine panel screens for eight drugs/drug classes: amphetamines, barbiturates, benzodiazepines, cocaine, marijuana, methadone, opiates, and PCP. The DOTS/NDEWS collaborating laboratory, the Division of Forensic Toxicology at the Armed Forces Medical Examiner System (AFMES), tested for 240 drugs or drug metabolites using liquid chromatography-tandem mass spectrometry (LC/MS/MS). See *DOTS Bulletin*, Issue 1, for a detailed description of the DOTS pilot study methodology (https://go.umd.edu/ndews-dots).

Sample Characteristics

Five of the eight patients presented as an overdose, one complained of intoxication, one complained of K2 use, and one was found down. These patients were between the ages of 23 and 56 years old, with half being younger than 40. Five were men, five were African American, and three were White. Four had a history of substance abuse, three had a history of both psychiatric disease and substance abuse, and one had a history of psychiatric disease. Four had been given naloxone by EMS personnel, and one had self-administered naloxone prior to arrival at the ED. Three of the eight were documented as being combative, and two required admission to the intensive care unit.

DOTS Drug Test Results

Table 1 shows the drugs or drug metabolites that were detected across the eight specimens. The most common substance found was the antihistamine diphenhydramine (N=5), followed by naloxone (4), morphine (4), and tramadol (4). Four tested positive for fentanyl and/or a fentanyl analog, three of which also tested positive for naloxone. Three of the four

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specimens that contained naloxone also contained buprenorphine, leading to the possibility that some had ingested a medication containing naloxone and buprenorphine. Noscapine (N=2), mCPP (1), and the synthetic cannabinoid 5F-ADB (1) were also found. Noscapine is an alkaloid found in raw opium and can potentiate the effects of morphine.[2,3] It is possible that the mCPP detected was taken separately or was present as a metabolite of trazodone; both were found in the same specimen. 5F-ADB is sold on the streets as synthetic marijuana (K2, Spice) and produces highs similar to cannabis at lower concentrations and can trigger psychotic episodes.[4] Seven specimens contained four or more drugs; five contained 8 to 17 drugs. One specimen had insufficient urine quantity to test for all of the drug panels and no drugs were detected by the remaining test panels for which there were sufficient urine quantity.

Implications

We found a wide array of substances in this convenience sample of ED patients presenting with apparent opioid overdose during a city-wide alert for atypical opioid overdoses. The prevalence of fentanyl and fentanyl analogs is striking, especially as Maryland has seen a 43-fold increase in fentanyl-related deaths over the last decade.[5]

Several drugs could potentially be responsible for the patients' overdose presentations, but no single agent linked all of the patients together, underscoring the difficulty clinicians face when attempting to treat these patients. The fact that most of these specimens contained eight or more drugs suggests that the number of drugs taken by these patients could be more important to their presentation and response to treatment than any one drug. After the precipitating event has been controlled, efforts should be made to diagnose and treat the patient's multiple drug use disorders.

The study results support our original suspicion of fentanyl involvement in these cases; however, little evidence was found for involvement of SC and none for synthetic cathinones. The prevalence of fentanyl in this sample of patients should prompt physicians to consider administering larger doses of naloxone to patients presenting with similar symptoms. Emergency physicians should plan ahead when these patients appear as multiple patients may present to the ED in rapid succession and they may require advanced respiratory support and admission to an intensive care unit. The prevalence of fentanyl will also help focus efforts to prevent overdose and educate patients. The ED may be a good setting for initiating, or referring to, drug treatment. Lastly, these results highlight the need for hospital drug screens to account for changing trends in drug use.

Limitations

This was a convenience sample of eight specimens obtained from patients coming to the ED for an apparent opioid overdose and is not representative of all ED patients. Because of unavoidable delays in initiating the DOTS pilot study procedures, the urines were tested approximately nine months after they were collected from the patients, and it is possible that some drugs degraded and went undetected. It is impossible to determine whether any of the detected drugs were taken under a doctor's supervision. It is also possible that some of the drugs detected were taken without the knowledge of the patient as a result of the manufacturing process and/or byproducts of unintended contamination.

References

1. Wish, E.D., Billing, A.S., Artigiani, E.E., Dezman, Z., Schwartz, B., & Pueschel, J. (forthcoming). *Drug early warning from re-testing biological samples: Maryland hospital study*. Office of National Drug Control Policy. Washington, DC: Executive Office of the President.
2. Harris E.A. (1965). The effects of noscapine and codeine on the ventilatory responses to excess of carbon dioxide and lack of oxygen. *British Journal of Pharmacology, 24*(2), 532–537.
3. Rida, P.C., LiVecche, D., Ogden, A., Zhou, J., & Aneja, R. (2015). The noscapine chronicle: A pharmaco-historic biography of the opiate alkaloid family and its clinical applications. *Medicinal Research Reviews, 35*(5), 1072–1096.
4. 5F-ADB Critical Review Report. (2017). *Expert Committee on Drug Dependence, 39th Meeting*. Geneva, Switzerland: World Health Organization.
5. Maryland Department of Health and Mental Hygiene. (2017). *Drug- and alcohol-related intoxication deaths in Maryland, 2016*. Baltimore: Maryland Department of Health and Mental Hygiene.

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Table 1: Drugs or Drug Metabolites Detected by DOTS/NDEWS Collaborating Laboratory Urinalyses

(*N* = 8 Urine specimens submitted to DOTS by the University of Maryland Medical Center, Midtown Campus Emergency Department)

	Common Drugs				Pharmaceutical Nonopioid Drugs																Nonfentanyl Opioids							Fentanyls				Other NPS[a]		
					Antihistamines				Benzodiazepines						Antidepressants																			SC[b]	
Specimen	Benzoylecgonine (cocaine)	THC (marijuana)	Methamphetamine	Amphetamine	Diphenhydramine	Promethazine	Cetirizine	Hydroxyzine	Alprazolam/α-Hydroxyalprazolam	7-Aminoclonazepam	Demoxepam	Nordiazepam	Oxazepam	Temazepam	Citalopram	Bupropion	Nortriptyline	Amitriptyline	Trazodone[c]	Naloxone	Quinine	Gabapentin	Morphine	6-Acetylmorphine (heroin)	Codeine	Tramadol	Noscapine	Methadone/EDDP	Buprenorphine/Norbuprenorphine	Fentanyl/Norfentanyl	FIBF (*para*-fluoroisobutyryl fentanyl)	*para*-Fluorobutyryl Fentanyl	Furanylfentanyl (Fu-F)	mCPP[c]	5F-ADB (metab 7)	Total Detected
1		✓			✓	✓						✓	✓	✓	✓					✓	✓		✓	✓	✓	✓			✓	✓	✓				17
2			✓	✓	✓				✓											✓	✓		✓			✓	✓	✓		✓	✓	✓	✓		✓	15
3					✓	✓	✓	✓	✓	✓	✓							✓	✓			✓							✓					✓		12
4	✓	*			✓		✓										✓				✓		✓				✓			✓	✓	✓				10
5	✓					✓			✓											✓			✓			✓			✓	✓					*	8
6																				✓						✓		✓	✓						4
7		*			✓		✓	✓								✓																				4
8	*			*	*	*	*	*	*	*	*	*	*	*	*	*	*	*			*	*	*	*	*	*	*		*						*	0
Total Positive:	2	1	1	1	5	3	3	2	3	1	1	1	1	1	1	1	1	1	1	4	3	1	4	1	1	4	2	3	3	4	3	3	1	1	1	

[a]NPS: New Psychoactive Substance.
[b]SC: Synthetic Cannabinoid.
[c]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.
*Specimen could not be tested for this drug/drug category because of insufficient urine quantity.

Source: Drug Outbreak Testing Service (DOTS), National Drug Early Warning System (NDEWS) Coordinating Center, Center for Substance Abuse Research, University of Maryland, College Park, May 2018.

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