FENTANYL SCREENING IN HOSPITALS

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INTRODUCTION

The availability of fentanyl and other synthetic opioids continues to increase across the country. With illegal drug markets being flooded with fentanyl, deaths are also rising. In 2022, provisional data from the Centers for Disease Control and Prevention found that 68 percent of the reported 107,081 drug overdose deaths that occurred in the U.S. in 2021 involved synthetic opioids other than methadone, with illicitly manufactured fentanyl appearing most often.[1]

One method for preventing overdoses from synthetic opioids is for health care providers to identify patients using such opioids prior to a fatal overdose event. Early identification allows providers to take appropriate harm reduction and outreach measures, such as providing the patient with opioid antagonists or presenting him or her with medication for addiction treatment options. An opportunity for detection and intervention can occur in a hospital emergency department (ED). Usually, when a patient arrives at the ED in an altered state, the health care provider orders a urine drug screen on the patient. Ideally, the results of the drug screen will inform the health care team of any substances the patient ingested and allow the team to establish a proper course of treatment; sometimes, however, drug screen results are unable to provide a complete picture, which can create gaps in care and missed opportunities for harm reduction and social services outreach.

In a 2018 study, researchers discovered that Baltimore-area EDs registered a decline in the percentage of intoxicated patients with positive drug screens for opiates, despite an increase in opioid-involved overdose deaths in the area. A subsequent study retested the urine samples of 76 patients evaluated in those EDs between February and April 2018 who presented with complaints of overdose or withdrawal or who sought substance use disorder treatment. Using a different toxicology testing method than that used for the original drug screen, the researchers discovered that 83 percent of the 76 patients retested had used fentanyl, but only 25 percent of those patients had an initial positive drug screen for opiates. These results suggested that fentanyl was more common in the Baltimore-area than previously suspected, but that its use was undetected among patients.

This fact sheet demonstrates why situations like that in Baltimore occur, what hospitals can do to better ensure the detection of fentanyl in the urine drug samples of ED patients, and what states are doing to make hospitals update their drug screen protocols.

DRUG SCREENS VERSUS CONFIRMATION TESTING

To be able to properly interpret and understand the value of toxicology results, it is necessary to understand the method of testing used. There are two general types of toxicology testing: presumptive testing by immunoassay, which is commonly referred to as a "drug screen," and confirmatory testing by gas or liquid chromatography.[2] A drug screen performed using immunoassay techniques uses antibodies to detect the presence of certain drugs

[1] Mbabazi Kariisa, et al., "Illicitly Manufactured Fentanyl–Involved Overdose Deaths with Detected Xylazine — United States, January 2019–June 2022," *Morbidity and Mortality Weekly Report* 72, no. 26 (June 30, 2023): 721–727, http://dx.doi.org/10.15585/mmwr.mm7226a4.

[2] Gas or liquid chromatography testing for conformation drug testing is always performed with mass spectrometry testing. Both forms of testing are needed for proper identification of a substance. For simplicity, the authors refer to gas or liquid chromatography/mass spectrometry testing as "chromatography."

and/or their metabolites[3] in a urine sample.[4] If the concentration of a drug is high enough in the urine, the instrument will alert the medical laboratory professional of a positive result for that particular drug class. Drug screens conducted by automated immunoassay instruments are available in most community hospitals and are typically the first test used to identify the presence of drug classes[5] in the urine. Most automated drug screens test for, at minimum, the five drug classes tested for in federal employees (known as the "Federal Five"): cannabis, cocaine, opiates, amphetamines, and phencyclidine (PCP).[6] However, many hospitals extend their drug screen panels to include additional drug classes, such as benzodiazepines and barbiturates. Immunoassay drug screens are relatively quick and inexpensive; however, these tests can result in false positives or false negatives.

Chromatography methods are generally used to confirm a positive drug screen result or definitively identify a detected substance. Unlike with a drug screen, chromatography detects the presence of specific drugs and/or metabolites in a patient's urine sample. Chromatography techniques are used to separate a mixture of chemical substances (*i.e.*, a urine sample containing drug compounds) into individual components. After the chemical substances are separated, they are individually identified by an instrument called a mass spectrometer, which measures the mass of different molecules within a sample. Because every drug has a unique mass, a computer algorithm can accurately identify the substance based on that information. Thus, stated simply, chromatography and mass spectrometry use is a process that identifies individual substances based on their molecular fingerprints. Chromatography testing offers several advantages over immunoassay drug screens, including better accuracy and having the ability to identify and confirm the presence of specific drugs in urine. However, there are barriers associated with chromatography that make this toxicology testing method impractical; namely, chromatography testing takes longer to produce results and is more costly compared to immunoassay drug screens. Additionally, specialized training is required to perform and analyze chromatography tests.

The differences between an immunoassay drug screen and confirmatory testing performed by chromatography can be more clearly seen through an example. Imagine that a health care provider orders a urine drug screen for a patient who recently used heroin. The drug screen results come back positive for opiates but include a disclaimer that the results of the drug screen are not definitive. Unfortunately, the drug screen does not inform the health care provider of the specific type of opiate the individual used. Moreover, it is worth noting that any other drug classes screened for in the drug screen panel that came up as either positive or negative are simply presumptive.[7] At most community hospitals and physicians' offices, this is the point at which the toxicology testing stops. Due to cost, staff shortages, and limited time to train staff on complex testing methodologies, many health care entities that offer drug screens cannot follow up a positive drug screen with chromatography testing to confirm the results. However, health care providers that have access to chromatography testing, mostly large academic medical centers, are able to retest the sample using chromatography. If this same patient's urine sample is tested using

[3] A metabolite is the product that remains after a drug is broken down (metabolized) by the body.
[4] In an immunoassay, reagents containing antibodies specific to certain drug classes are added to a urine sample. If the sample contains a drug, antibodies specific to that drug class will bind to the drug. The laboratory instrumentation determines the concentration of antibodies binding with drugs in the person's sample. If the concentration reaches a certain threshold, then the instrument will flag the sample as positive.
[5] A drug class is a set of drugs that have similar chemical structures, the same mechanism of action, or a related mode of action (*e.g.*, opiates, benzodiazepines, amphetamines, and the like).
[6] 49 C.F.R. § 40.85 (2018).
[7] Confirmatory testing would be needed to rule out the possibility of false negative or false positive results.

chromatography, the results can definitively inform the health care provider which substance(s) the individual used. In this case, chromatography would reveal that the urine of an individual who used heroin recently contains 6-monoacetylmorphine and morphine (*i.e.*, two metabolites of heroin). Based on those results, the health care provider can definitively say the patient used heroin.

THE PITFALLS OF DRUG SCREENS

Drug screens are prone to false positive and false negative results. False positive drug screens tend to be somewhat common and occur when a substance cross-reacts with the immunoassay. For example, if an individual has ingested pseudoephedrine, a common ingredient in cold medicine, and then a drug screen is administered, he or she will likely screen positive for amphetamines. False positive drug screen results can be explained by performing a proper medication history on the patient, including any over-the-counter medications, herbs, and supplements, in order to identify any cross-reactive substances. False negative results with immunoassays, on the other hand, are more difficult to detect as evidenced by the Baltimore-area study mentioned above, in which significant fentanyl use was initially undetected.

A common reason for false negatives in drug screens is that the screen is unable to detect the drug ingested by the individual because the panel used does not include that specific drug. This results in health care providers missing the full clinical picture regarding the substances ingested by the patient. To better understand false negatives, it is necessary to understand for what drugs a particular drug screen panel actually tests. All drug screens test for opiates, and a drug screen will flag positive for opiates if the urine sample contains codeine or morphine. However, most commonly available drug screens do not readily detect semisynthetic opioids, like oxycodone, or synthetic opioids, such as fentanyl and methadone. To address this problem, many clinical laboratories add oxycodone and methadone testing to their drug screen panels in order to screen for a broader array of opioids. However, these additions are not enough to provide a comprehensive drug screen in today's drug landscape.

Drug use patterns in a community can change rapidly, to the point that it is impossible for clinical toxicology testing to keep up. It can be said that current clinical toxicology panels reflect the drug epidemics of the past more than the current drug landscape. For example, PCP, which is part of the "Federal Five," gained popularity in the illicit drug market in the 1960s with widespread use peaking in the 1980s. After the 1980s, PCP use decreased substantially; however, some hotspots of PCP use remain. According to the 2022 National Survey of Drug Use and Health, 204,000 individuals aged 12 and older admitted to using PCP in the past year.[8] This is significantly lower than the number of individuals aged 12 and up who used cocaine (5,274,000), heroin (1,049,000), or methamphetamine (2,705,000) in the past year.[9] This is not to suggest that PCP should be removed from the "Federal Five" or no longer screened for by hospital laboratories, but merely to emphasize the constant changes in the illicit drug landscape and the need to expand and modify drug screen panels over time to address the changes in the market.

ADDRESSING THE DRUG SCREEN PROBLEM

The high frequency of fentanyl use across the country suggests that regular fentanyl screening as part of hospital drug screens is needed to address a gap in patient care. In August 2022, only five percent of ED encounters for overdose included a screening test for fentanyl.[10] By the end of June 2023, the number increased to 14 percent.[11]

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[8] 2022 National Survey of Drug Use and Health, *Substance Abuse and Mental Health Services Administration*, Table 1.1A, available at https://www.samhsa.gov/data/sites/default/files/reports/rpt42728/NSDUHDetailedTabs2022/NSDUHDetailedTabs2022/NSDUHDetTabsSect1pe2022.htm.

[9] *Id.*

[10] "Fentanyl Toxicology Screenings for Overdoses on the Rise," Epic Research, last modified August 18, 2023, https://epicresearch.org/articles/field-note-fentanyl-toxicology-screenings-for-overdoses-on-the-rise.

[11] *Id.*

While the percentage of hospitals offering fentanyl screening is increasing, the vast majority of hospitals are still not offering the test. The failure to test for fentanyl prevents health care providers from seeing a patient's full clinical picture and can lead to mismanaged care. With polydrug use on the rise, it is important for health care providers to realize that single-substance drug use is becoming rare. For example, a patient who screens positive for cocaine is likely to also have fentanyl in his or her system, as stimulants are increasingly being combined with opioids. The percent of U.S. overdose deaths involving fentanyl and stimulants increased from 0.6 percent in 2010 to 32.3 percent in 2021.[12] Furthermore, health care providers cannot rely on patients to accurately disclose what substances they ingested because there are high rates of counterfeiting and contamination in substances of which a patient may be unaware. A patient may have consumed what he or she believed to be a Percocet or Xanax pill without realizing that the pill was a counterfeit containing fentanyl.

Based on their findings, the researchers in the Baltimore-area study recommended that hospital laboratories adapt their drug screens to detect fentanyl. Adding fentanyl to their drug screen panels requires laboratories to invest in additional reagents[13] for their immunoassay instrument, as well as quality control samples[14] and calibrators.[15] These reagents, controls, and calibrators cost thousands of dollars and must be replenished at additional cost every few months. Nevertheless, these costs are more financially feasible than the large capital investment needed for chromatography and mass spectrometry instrumentation. While many laboratories operate on a limited budget, there is value in investing in fentanyl screening capabilities, especially in areas with a high prevalence of fentanyl use and overdoses involving fentanyl. Other than the time needed to validate the fentanyl assay, the addition of fentanyl as part of the laboratory's drug screen should not affect staffing or workflow issues, as the assay is being added to a drug screen panel that already exists.

In late January 2019, the University of Maryland Medical Center initiated routine fentanyl screening for all patients undergoing urine drug screening. In an analysis of drug screens performed at the hospital from this time through December 2019, 83 percent (340 of 408) of patients tested positive for fentanyl. Of those 340 patients, 55 percent (186) tested negative for opiates. These results show the importance of adding fentanyl to a drug screen panel to ensure a complete clinical picture of the patient's drug consumption. It is important to note, however, that immunoassays validated for fentanyl might not be able to detect all of the fentanyl analogs. Moreover, because a fentanyl immunoassay is a drug screen and not chromatography, it cannot definitively determine the presence of fentanyl in a urine sample.

Ideally, a positive urine drug screen would be followed up with a confirmatory test, but it is not feasible for every hospital to implement and perform chromatography/mass spectrometry testing. Many community hospitals lack the funds, infrastructure, and personnel to establish and operate confirmatory drug testing. In situations where a hospital or health care provider does not have the ability to perform chromatography in-house, there is the option to send the sample out to a reference laboratory for testing. While this presents a good alternative for entities that cannot perform confirmatory testing in-house, it is impractical to send out every urine drug sample for confirmatory testing. Additionally, "send-out testing" is expensive and, on average, takes several days to obtain the results. The decision to send a sample out should be determined by the patient's clinical care team, considering

[12] Joseph Friedman and Chelsea L. Shover, "Charting the fourth wave: Geographic, temporal, race/ethnicity and demographic trends in polysubstance fentanyl overdose deaths in the United States, 2010–2021" *Addiction* 118, no. 12 (Sept. 13, 2023): 2477-2485, https://doi.org/10.1111/add.16318.

[13] A reagent is a substance or mixture used in a chemical analysis.

[14] Quality control samples are non-patient samples with a known value and are tested regularly to ensure that the instrument is providing accurate results.

[15] Calibrators are used to calibrate an instrument. Calibration is the process of configuring an instrument to provide results within an accurate range.

the clinical presentation of the patient, the patient's medical and substance use history, and the drug landscape of the surrounding area.

STATE ACTION TO REQUIRE FENTANYL SCREENING IN HOSPITALS

In August 2022, California became the first state to enact a law requiring general acute care hospitals that conduct urine drug screens to include testing for fentanyl as part of their drug screen panel. The law, which became effective on January 1, 2023, is colloquially referred to as "Tyler's Law."[16] Tyler Shamash, after whom the law is named, experienced a non-fatal overdose in 2018 and received a drug screen while in the hospital ED. His mother asked the doctor if Tyler had been tested for fentanyl, and the doctor informed her that fentanyl did not come up positive on his toxicology screen. Unbeknownst to the doctor, the hospital's drug screen did not screen for fentanyl. Tyler overdosed again the next day and died, and the coroner's toxicology report indicated that he had fentanyl in his system.

Maryland enacted a law similar to that of California in May 2023, which went into effect on October 1, 2023 and is known as the "Josh Siems Act."[17] Josh Siems died of an overdose in 2022, and his family was surprised to hear that his hospital drug screen only tested positive for cocaine, despite fentanyl being found in his apartment. The Siems family, like the Shamash family, would later learn that the hospital's toxicology screen did not include fentanyl. Additionally, Pennsylvania signed a similar bill into law in December 2023.[18] Pennsylvania's law requires a hospital to include xylazine as part of its drug screen panel as well, "if testing is available as part of a urine drug screen panel." As of this writing, however, no U.S. Food and Drug Administration approved xylazine reagents compatible with the commercially available immunoassay chemistry analyzers used by hospitals to perform routine urine drug screens exist. In addition to California, Maryland, and Pennsylvania's laws requiring fentanyl to be included in a hospital's routine drug screen, four states (Michigan,[19] New Jersey,[20] New York,[21] and North Carolina[22]) have introduced bills to enact a similar law. In addition to the actions being taken by some states, U.S. Senators Joe Manchin (D-WV) and Mike Braun (R-IN) introduced a bill in December 2023 that directs the U.S. Department of Health and Human Services (HHS) to provide hospitals with guidance on how emergency rooms can implement fentanyl testing in their routine drug screens.[23] Specifically, the bill requires HHS to complete a study to determine: (1) how frequently hospital emergency departments test for fentanyl; (2) the costs associated with such testing for fentanyl; (3) the potential benefits and risks for patients receiving such testing for fentanyl; and (4) how fentanyl testing in hospital emergency departments may impact the experience of the patient.[24] Upon completion of the study, HHS would be required to issue guidance on whether hospital emergency departments should implement fentanyl testing as a routine procedure for patients who experience an overdose; and how hospitals can ensure that hospital emergency department clinicians are aware of the substances which are tested for in routinely-administered drug tests, regardless of whether those tests screen for fentanyl.[25] Ideally, a hospital would add fentanyl to its routine urine drug screen panel without the need for government intervention, but laws such as those in California, Maryland, and Pennsylvania help to ensure that all hospitals throughout the state perform drug screens that include fentanyl.

[16] CAL. HEALTH & SAFETY CODE § 1259.3 (West 2023).
[17] MD. CODE ANN., HEALTH-GEN. § 19-308.9 (West 2023).
[18] 2023 Pa. Laws 43.
[19] H.B. 5113, 102nd Leg, Reg Sess. (Mich. 2023).
[20] S.B. 3789, 220th Leg., Reg. Sess. (N.J. 2023).
[21] S.B. 6085, 2023-2024 Leg., Reg. Sess. (N.Y. 2023)
[22] H.B. 745, 2023-2024 Gen. Assemb., Reg. Sess. (N.C. 2023).
[23] S. 3519, 118th Cong. (1st Sess. 2023).
[24] *Id.*
[25] *Id.*

CONCLUSION

Despite fentanyl use becoming widespread across the country, most hospital laboratories do not routinely test for fentanyl as a part of their drug screen panels. While chromatography is the gold standard for toxicology testing and can identify a much wider variety of substances that a person might have consumed, it is not feasible for this method to be implemented everywhere. Additionally, it would be cost-prohibitive to test every patient using this method. The cost-effective solution to this issue is for entities that perform immunoassay drug screens to add fentanyl to their drug screen panels, like the University of Maryland Medical Center did in January 2019 after learning that fentanyl consumption was going undetected in their patients. States also have the ability to enact laws requiring hospitals to update their drug screen panels to include fentanyl. Screening for fentanyl will provide health care providers with a clear clinical picture and allow for the implementation of more effective treatments.

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