ORIGINAL ARTICLE

Definitive urine drug test findings in patients prescribed opioids for pain from a large national database

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ABSTRACT

Objective: *Clinicians and policymakers have been wrestling with the appropriateness and safety of opioid therapy during the opioid crisis. Policy and clinical decisions have often been made without much current data on trends in drug use in patients with pain. Thus, we evaluated definitive urine drug test (UDT) results in patients being treated for pain to see if those taking their prescribed opioids were less likely to be positive for the primary illicit drugs currently driving overdose deaths: cocaine, heroin, fentanyl, and methamphetamine.*

Design, setting, and patients: *A cross-sectional study of UDT results from January 1, 2015 to September 30, 2021, from 600,000 patient specimens submitted for testing by pain management specialists.*

Interventions: *UDT by liquid chromatography-tandem mass spectrometry as ordered by the treating clinician.*

Main outcome measures: *Presence of other substances stratified by whether a patient's prescribed opioid was found.*

Results: *The presence of cocaine, heroin, fentanyl, and methamphetamine for the total population was low (<5 percent). Of the 347,092 patients prescribed opioids, 76 percent (n = 264,961) were positive on UDT for their prescribed opioid ("consistent"). Compared to patients without their prescribed opioid present ("inconsistent"), patients consistent with therapy were 54 percent (incidence rate ratio (IRR) 1.54, 95 percent confidence interval (CI) 1.47-1.59) less likely to be positive for cocaine, 47 percent [IRR 1.47, 95 percent CI 1.34-1.57] less likely to be positive for heroin, and 35 percent [IRR 1.35, 95 percent CI 1.24-1.45] less likely to be positive for methamphetamine, $p < 0.001$. Differences between the groups for fentanyl were not significant.*

Conclusions: *Overall positivity rates for cocaine, heroin, fentanyl, and methamphetamine were low. Patients with prescribed opioid present were less likely to be positive for cocaine, heroin, or methamphetamine. Patterns of substance use within this pain management population should be used to inform ongoing policy decisions.*

INTRODUCTION

After a steady increase in the early 2000s, prescribing of opioid analgesics has declined 44 percent over the past decade.[1] While some patients benefited from more liberal prescribing of opioids, reporting improved functionality and quality of life from pain control,[2] this expansion is considered by many to be directly linked to the beginning of the drug overdose crisis that continues to exist in the United States today. Between 1999 and April 2021, approximately 600,000 people died from an

overdose involving any opioid, including prescription and illicit opioids.[3,4] This "overdose epidemic" has been characterized by three distinct "waves," beginning in 1999 with a rise in overdose deaths primarily attributed to prescription opioid analgesics.[3] It is believed that in addition to prescribing practices, several other factors contributed to this rise in a complex fashion, which have been well-characterized elsewhere.[5]

In 2010, heroin became the leading cause of opioid-involved overdose deaths, signaling the start of the second "wave," and in 2013, while heroin-involved overdose deaths were still on the rise (peaking in about 2017), the third "wave" began, involving synthetic opioids, primarily, illicitly manufactured fentanyl (IMF), which the Drug Enforcement Administration (DEA) currently calls the "primary driver behind the opioid crisis."[3,6] It appears that a new fourth "wave" of overdose fatalities is now emerging as methamphetamine use rises, and along with it, psychostimulant-involved overdose deaths[7,8] (Figure 1).

The variety of substances driving each of these "waves" of the overdose epidemic presents unique challenges that require targeted solutions. For example, risk mitigation efforts intended to reduce harm associated with prescribed opioids differ in some respects from approaches used to curb IMF and methamphetamine. In 2011, just after the start of the second wave, the Centers for Disease Control and Prevention (CDC) declared the steady increase in deaths due to prescription opioids to be an "epidemic," and it seemed clear that a change was needed.[1] Various measures were proposed, including those intended to decrease opioid prescribing; implementation of state databases to track prescribing and medication-seeking behavior—Prescription Drug Monitoring Programs (PDMPs)—increased dissemination of naloxone to reverse opioid-induced respiratory depression, and a significant increase in prescriber education.[9] In 2016, CDC Guidelines for Prescribing Opioids for Chronic Pain were published with the intention of providing guidance to nonexpert clinicians prescribing opioids for chronic pain.[10] In some cases, these guidelines were adopted as policy by state medical boards. Unfortunately, as some of the authors later acknowledged in the *New England Journal of Medicine*, these guidelines resulted in unintended consequences for patients with chronic pain.[11] This

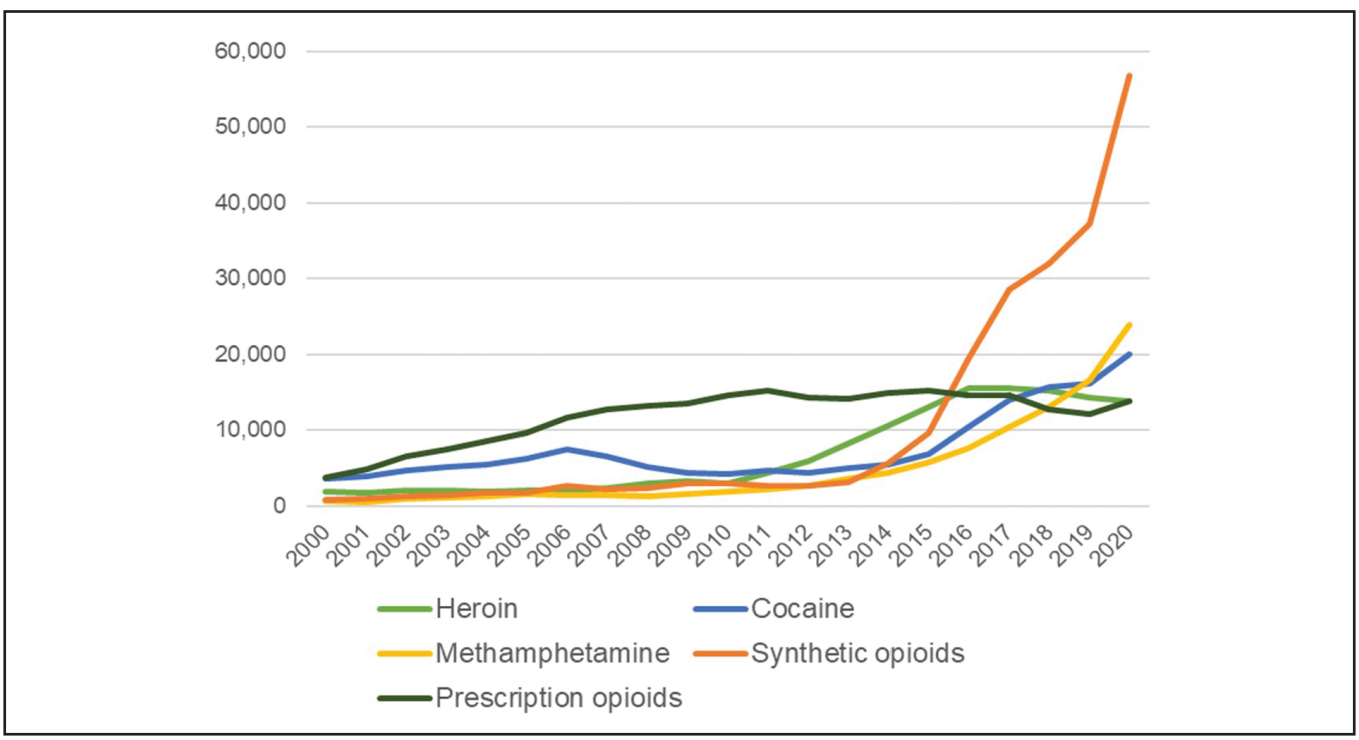

Figure 1. The four waves: drug overdose deaths by drug or drug class.
Source: Provisional Drug Overdose Death Counts: National Center for Health Statistics. Available at *https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm*. Accessed January 2022.

included the misapplication outside of the intended patient population, the implementation of dose ceiling limits, forced tapering or abrupt discontinuation of the opioids, and some clinicians no longer wishing to prescribe opioids to patients on long-term therapy or even dismissing patients from their practices.[11,12] In 2020, the American Medical Association (AMA) wrote an open letter to the CDC describing recommended revisions to these guidelines, stating "we can no longer afford to view increasing drug-related mortality through a prescription opioid-myopic lens" and calling for a "broad-based public health approach [to the overdose epidemic]."[12] As of 2021, the CDC began the process of re-evaluating and possibly revising these guidelines, but at the time of this writing, it is unclear what, if any, changes might be included.

At this point, it appears that regulatory changes created to combat the overdose epidemic by decreasing the number of prescriptions written and opioids dispensed have not resulted in a decrease in overdose deaths. Drug overdose deaths continue to reach record highs, despite an overall decline in *prescription* opioid-involved deaths since 2017.[13,14] Additionally, Substance Abuse and Mental Health Services Administration survey data also show a decline in the nonmedical use of prescription opioids.[15,16] It would seem prudent that to maintain access to opioids for people who need them, a reconsideration of the approach to facilitate safe and effective prescribing of opioid analgesic therapy should include evaluating timely data streams of aberrant substance use patterns in populations with and without chronic pain. There are very few, if any, recent studies investigating aberrant substance use in an opioid-treated population of patients with chronic pain. Cheatle et al. demonstrated that primary care patients with chronic pain, who were carefully screened via several measures to identify comorbid psychiatric diagnoses, functional impairment, and substance use disorders (SUDs), had low rates of problematic substance use and almost no aberrant behaviors when treated with opioid medications.[17] Additionally, a chart review of urine drug test (UDT) results performed primarily by immunoassay testing (with its known limitations[18]), suggested that 37 percent of patients with pain prescribed opioids had test results indicating illicit substance use and/or medication misuse. While this study was published recently, the UDT results were obtained between 2014 and 2016 and may not characterize today's opioid-treated patients with pain.

Definitive UDT results can offer a source of data about substance use in the clinical setting. UDT is recommended by professional guidelines as part of a comprehensive monitoring plan for patients prescribed opioids[10,19] and can provide objective information about a patient's recent use of substances and help clinicians make more informed decisions about mitigating risk, including initiating counseling with a patient on overdose prevention strategies.[20] UDT may also help a clinician better manage a patient's treatment with controlled substances, identify SUD earlier in the pain management setting, and help them advocate for patients on opioid therapy.[21] In addition to its clinical utility, aggregated, definitive UDT data can be used as a data stream to quickly identify and track drug use trends as well as identify factors influencing positivity and allow for examination of these issues on a large scale and in a geographically diverse population of people.[22-24]

Recent research characterizing drug use trends in a pain management patient population is lacking. Thus, in this study, we examined trends from a proprietary national database of definitive UDT results from patients prescribed opioids in a pain management specialty setting. We also briefly examined the potential overlay of the COVID-19 pandemic on these results from March 2020 to March 2021.

METHODS

Data source and sample selection

We conducted a retrospective study of UDT results from January 1, 2015 to September 30, 2021, from patient specimens submitted for testing by healthcare practices specializing in pain management. Specimens from patients over 18 years old were collected from healthcare practices from 49 states (Vermont and Washington, DC were not represented). Each UDT was individually ordered by the clinician based on medical necessity. A single specimen for each patient was selected based on the earliest specimen collection date, and repeated measurements for the same patient were removed from the sample analysis. The study used a sample of 600,000 randomly selected patient specimens from Millennium Health's proprietary UDT database. Specimens were analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS)

for each analyte. The LC-MS/MS testing method is a laboratory-developed test with performance characteristics determined by Millennium Health, San Diego, California, which is certified by the Clinical Laboratory Improvement Amendments and accredited by the College of American Pathologists for high-complexity testing. The study protocol was approved by the Aspire Independent Review Board and includes a waiver of consent for the use of deidentified data. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.

Prescribed opioid urine drug testing

We examined definitive UDT results for five commonly prescribed opioids. Out of the 600,000 unique patient urine specimens, 347,092 specimens were from patients who were prescribed at least one of the following five opioids and tested for that opioid based on the ordering clinician's determination of medical necessity (drugs and metabolites tested in parentheses): fentanyl (fentanyl, norfentanyl), hydrocodone (hydrocodone, norhydrocodone), morphine, oxycodone (oxycodone, noroxycodone), and tramadol (tramadol, *N*-desmethyl-tramadol, and *O*-desmethyl-tramadol). Although the laboratory typically tests hydromorphone and oxymorphone as metabolites of hydrocodone, morphine, and oxycodone, we removed these analytes to avoid confounding with use of the prescription drugs hydromorphone or oxymorphone. We excluded patients prescribed more than two opioids concurrently; in a previous analysis with a randomly selected 600,000 specimens from the same population, >98 percent had only one or two opioids prescribed, which is consistent with typical clinical practice. Since not all specimens were tested for each analyte, we calculated rates out of all specimens tested for the analyte (number of ordered tests, and prescription rates for each analyte shown in Table 1). A global opioid drug class was constructed to include specimens reported to be prescribed any of the five opioids.

The opioid class was divided into two subgroups for analysis: "consistent" and "inconsistent." The consistent group was defined as having at least one of the opioids prescribed to the patient as positive on UDT. For example, if a patient was prescribed oxycodone and the specimen was positive for any analyte tested for oxycodone, eg, oxycodone and/or noroxycodone,

Table 1. Characteristics of urine drug test specimens tested between January 1, 2015 and September 30, 2021

Characteristics	Frequency, n (percent)
Unique patient specimens	600,000 (100.00)
Sex	
F	342,083 (57.01)
M	257,917 (42.99)
Age	
Age, median [IQR]	55 [36-74]
18-24	7,129 (1.19)
25-34	47,646 (7.94)
35-44	93,642 (15.61)
45-54	144,474 (24.08)
55+	307,109 (51.18)
US census division	
East North Central	116,058 (19.34)
East South Central	63,148 (10.52)
Mid Atlantic	51,767 (8.63)
Mountain	105,145 (17.52)
New England	13,980 (2.33)
Pacific	52,885 (8.81)
South Atlantic	133,746 (22.29)
West North Central	10,735 (1.79)
West South Central	52,536 (8.76)
UDT specimens with prescribed and ordered opioid tests	
Opioids	347,092 (57.85)
Fentanyl	14,180 (2.36)
Hydrocodone	158,964 (26.49)
Morphine	47,310 (7.89)
Oxycodone	140,472 (23.41)
Tramadol	52,906 (8.82)
UDT specimens with ordered nonprescribed and/or illicit drug tests	
Cocaine	520,489 (86.75)
Fentanyl	485,159 (80.86)
Heroin	497,866 (82.98)
Methamphetamine	451,950 (75.33)

IQR: interquartile range.

it would fall into the consistent group. If a patient was prescribed oxycodone and hydrocodone and the specimen was only positive for oxycodone or noroxycodone, it was categorized into the consistent group. The inconsistent group was defined as negative for all analytes tested for the prescribed opioid(s) (Figure 1). Essentially, we created a variable that reflects consistent vs inconsistent findings with regard to the patients' prescribed opioids as a proxy for adherence issues, while acknowledging the limitations for this method.

Nonprescribed and illicit urine drug testing

We stratified results into consistent or inconsistent and evaluated the likelihood of each group being positive for either an illicit or nonprescribed substance. We define "nonprescribed substance" as a commercially available therapeutic product that is being detected in a specimen from a patient without a reported prescription for that product. The following drugs and/or drug classes were tested for in a subset of patient specimens based on the ordering clinician's determination of medical necessity (drug and metabolites tested in parentheses): cocaine (benzoylecgonine), fentanyl (fentanyl and norfentanyl), heroin (6-monoacetylmorphine), and methamphetamine. If any parent analyte or metabolite was detected, the drug of interest was considered positive for that specimen. We excluded positive results for medications that were reported by clinicians to be currently prescribed to patients (for example, if a patient was reported to be prescribed methamphetamine, eg, Desoxyn®, we did not count them for methamphetamine positivity).

Covariates

Additional characteristics for each specimen included the patient's sex, age (discretized into 18-24, 25-34, 35-44, 45-54, and ≥55-year-olds), and location of the healthcare provider (nine major US census divisions) were also collected.

Statistical analysis

Annual trends in crude positivity rates were calculated as the percentage of tests that were positive in the sample in each year from 2015 to 2021 (January through September 2021). Clopper–Pearson 95 percent binomial confidence intervals (CIs) were estimated for the raw positivity rates. These rates and CI values were calculated per year and stratified by opioid class detection (consistency).

Poisson regression was performed to evaluate the association of demographic features and opioid detection with nonprescribed and/or illicit drug detection. Collection year, clinic location (US census division), sex, age, and opioid detection (consistent or inconsistent) were modeled as discrete explanatory variables. Collection year and opioid detection were modeled in an interaction effect. All parameters were estimated using robust sandwich estimators to correct for mild distributional violations. Poisson regression was used due to the focus on incidence rate ratios (relative risk) and rates. Log-binomial models were also attempted; however, convergence failures caused us to move to Poisson models.[25] Adjusted incidence rates (Least Square Mean), adjusted incidence rate ratios (aIRR), Sidak-corrected 95 percent CI values and Tukey-corrected p values were estimated. In the case of the illicit fentanyl model, prescribed fentanyl detection was not evaluated in the context of the global opioid class.

Poisson regression was also used to evaluate whether the March 13, 2020 declaration of COVID-19 as a national emergency in the United States[26] was associated with drug positivity changes in the pain management population stratified by consistency with opioid therapy. Year over year change was evaluated for each of the four illicit drugs based on collection before COVID-19 (March 13, 2019–March 12, 2020) and collection after the declaration (March 13, 2020–March 12, 2021). Collection date (pre-COVID-19 vs COVID-19) and opioid detection were modeled as an interaction effect. Clinic location (US census division), sex, and age were modeled as discrete covariates. Pre-COVID-19 vs COVID-19 aIRR was estimated and stratified by opioid class detection using the interaction term.

R statistical software version 4.0.2 (R Project for Statistical Computing) was used for data analysis. Statistical significance was set at p value less than .05, and all tests were two-tailed.

RESULTS

Study population demographics

Six-hundred thousand definitive UDT results from patients in pain management practices, with samples collected between January 1, 2015 and September 30, 2021, were analyzed (Table 1). The sample population was 57.01 percent female with a median age

(interquartile range) of 55 (36-74) years old. The greatest number of specimens were from the South Atlantic (22.29 percent) and East North Central (19.34 percent) US census divisions (Table 1).

We examined the presence of these five commonly prescribed opioids in urine: fentanyl, hydrocodone, morphine, oxycodone, and tramadol. Out of 600,000 specimens, 347,092 were reported to be prescribed at least one of these opioids with accompanied ordered tests. Oxycodone and hydrocodone were the most prescribed and ordered (Table 1). Out of the 347,092 prescribed these opioids, 264,961 (76.34 percent) were consistent on UDT with their prescribed opioid (Figure 2).

In addition to prescribed opioids, four additional illicit drugs were evaluated: cocaine, fentanyl, heroin, and methamphetamine. While testing for these drugs was not ordered in all 600,000 specimens, all four drugs were ordered for testing at similar rates (range 75.33-86.75 percent), with cocaine most ordered (Table 1).

Detection of illicit drugs

Generally, the study population had a low rate of overall positivity for cocaine, heroin, methamphetamine, and fentanyl, and patients with their prescribed opioid negative on UDT (defined above as inconsistent) were more likely to be positive for cocaine, heroin, or methamphetamine.

We evaluated raw positivity rates for each year for the illicit substances and stratified them by the total sample population and whether the patient was consistent or inconsistent for a prescribed opioid (Table 2). Generally, raw positivity rates for the total sample population (including those not prescribed or tested for the opioids of interest) were low for the four illicit substances of interest, with cocaine having the highest positivity rate (ranging from 1.76 percent in 2019 to 3.07 percent in 2015) and heroin having the lowest positivity rate (ranging from 0.13 percent in 2021 to 0.73 percent in 2015) (Table 2). The group negative for their prescribed opioid, defined above as the inconsistent group, had higher positivity rates than the consistent group for cocaine, heroin, and methamphetamine in all years. Fentanyl positivity was roughly the same for the inconsistent group as the consistent group, until 2020 through 2021.

We used Poisson regression and aIRR to evaluate whether a patient inconsistent was more likely to be positive for a nonprescribed or illicit drug

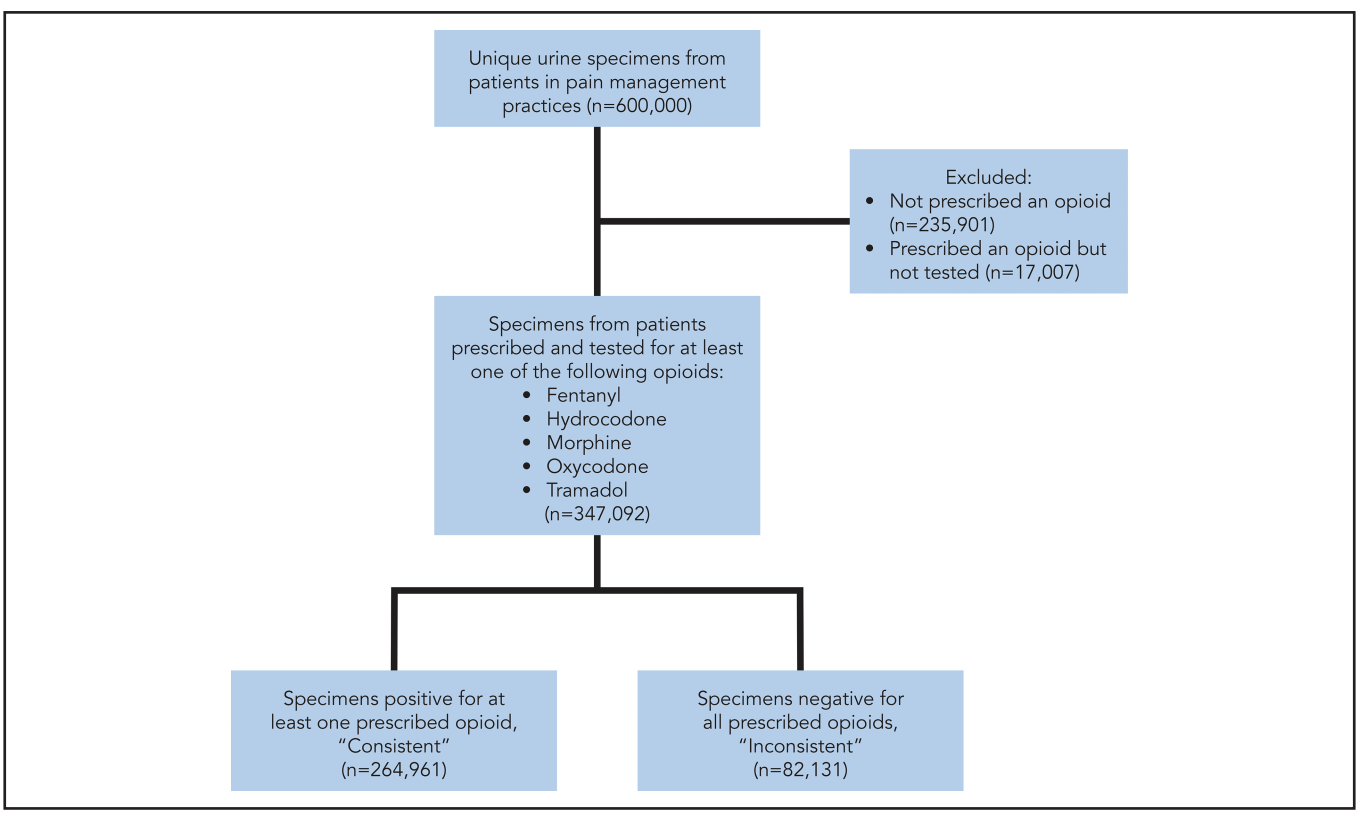

Figure 2. Classification of specimens into consistent versus inconsistent for prescribed opioid status.

Table 2. Nonprescribed and/or illicit raw drug positivity rates (percent [95 percent CI])* per year stratified by consistent versus inconsistent

Drug	Group†	2015	2016	2017	2018	2019	2020	2021‡
Cocaine	Rx opioid inconsistent	4.18 [3.90-4.47]	3.60 [3.28-3.94]	3.33 [3.01-3.68]	2.88 [2.56-3.23]	2.19 [1.89-2.52]	2.53 [2.11-3.01]	2.16 [1.73-2.67]
Cocaine	Rx opioid consistent	1.85 [1.73-1.97]	1.81 [1.68-1.95]	1.55 [1.42-1.68]	1.16 [1.05-1.29]	1.07 [0.94-1.20]	0.98 [0.82-1.15]	1.15 [0.97-1.35]
Cocaine	Total sample population	3.07 [2.98-3.16]	2.93 [2.83-3.04]	2.58 [2.48-2.69]	1.99 [1.89-2.09]	1.76 [1.66-1.87]	1.83 [1.70-1.97]	1.88 [1.74-2.03]
Fentanyl	Rx opioid inconsistent	0.85 [0.72-1.00]	0.92 [0.76-1.10]	0.88 [0.71-1.07]	0.85 [0.68-1.05]	0.75 [0.58-0.96]	1.41 [1.10-1.79]	1.96 [1.54-2.46]
Fentanyl	Rx opioid consistent	0.87 [0.78-0.96]	0.92 [0.82-1.02]	0.83 [0.74-0.94]	0.82 [0.72-0.93]	0.86 [0.75-0.99]	1.10 [0.93-1.29]	1.17 [0.99-1.38]
Fentanyl	Total sample population	1.48 [1.41-1.55]	1.56 [1.48-1.64]	1.54 [1.46-1.63]	1.30 [1.21-1.38]	1.32 [1.23-1.41]	1.77 [1.63-1.91]	1.79 [1.64-1.94]
Heroin	Rx opioid inconsistent	0.91 [0.77-1.07]	0.57 [0.45-0.72]	0.41 [0.30-0.55]	0.25 [0.16-0.37]	0.21 [0.13-0.34]	0.21 [0.10-0.38]	0.16 [0.06-0.34]
Heroin	Rx opioid consistent	0.35 [0.29-0.40]	0.26 [0.21-0.31]	0.19 [0.14-0.24]	0.10 [0.07-0.15]	0.08 [0.05-0.13]	0.05 [0.02-0.11]	0.07 [0.03-0.13]
Heroin	Total sample population	0.73 [0.68-0.78]	0.58 [0.53-0.63]	0.47 [0.42-0.52]	0.30 [0.26-0.35]	0.25 [0.21-0.29]	0.26 [0.21-0.32]	0.13 [0.09-0.17]
Methamphetamine	Rx opioid inconsistent	2.13 [1.92-2.35]	2.56 [2.25-2.90]	2.04 [1.77-2.35]	2.17 [1.86-2.50]	1.62 [1.35-1.93]	1.44 [1.11-1.83]	1.74 [1.34-2.23]
Methamphetamine	Rx opioid consistent	1.28 [1.18-1.38]	1.37 [1.24-1.51]	1.13 [1.01-1.26]	0.86 [0.75-0.98]	0.88 [0.76-1.01]	1.03 [0.86-1.22]	0.92 [0.75-1.11]
Methamphetamine	Total sample population	1.86 [1.79-1.94]	2.47 [2.36-2.59]	2.05 [1.94-2.15]	1.93 [1.82-2.04]	2.00 [1.89-2.12]	2.02 [1.87-2.18]	1.68 [1.54-1.83]

*95 percent CI calculated using exact binomial intervals.
†Group: Rx opioid inconsistent group refers to specimens prescribed an opioid but with negative test results for all opioids. Rx opioid consistent group refers to specimens prescribed an opioid and with positive test results for at least one corresponding opioid. Total sample population group refers to the entire sample population, regardless of prescription opioid status.
‡2021 data extend through September 30, 2021.

when compared to a consistent patient. The pattern found in the raw data was maintained after adjustment by covariates. Generally, patients with results inconsistent with their prescribed opioid therapy were more likely to be positive for an illicit drug over the 5 years evaluated, specifically for cocaine or methamphetamine (Figure 3 and Table 3). From 2015 to 2021, those inconsistent for a prescribed opioid were about twice as likely to be positive for cocaine compared to those consistent with therapy (aIRR range 1.87-2.16). For methamphetamine, the difference was significant every year except 2020, with the inconsistent group being up to approximately 2.5 times as likely to be positive for methamphetamine (aIRR range 1.55-2.35, Table 3). They were also more likely to be positive for heroin, but this did not reach statistical significance except in 2015 (aIRR 1.88, $p < 0.001$); this may be due to a reduction in power due to decrease in heroin use over time. Differences between the groups for fentanyl were not significant.

We also analyzed the effects of the covariates individually (sex, age, US census division, and whether consistent or inconsistent with prescribed therapy [main effect]) to evaluate how they affected the likelihood of positivity for the four illicit drugs (Table 4). We found that those least likely to be positive for any of the four illicit drugs were female and aged 55 or older. Across the examined timeframe, those found to be inconsistent with their prescribed opioid on UDT were 1.54 times more likely to be positive for cocaine, 1.47 times more likely to be positive for heroin, and 1.35 times more likely to be positive for methamphetamine ($p < 0.001$ for each); there was no significant difference in the likelihood to be positive for illicit fentanyl between the two groups (Table 4).

Finally, we analyzed the entire population for illicit substance use when all four tests (cocaine, heroin, fentanyl, and methamphetamine) were ordered by the treating clinician. The majority of the population (95.39 percent) was negative for all four illicit substances of interest (data not shown).

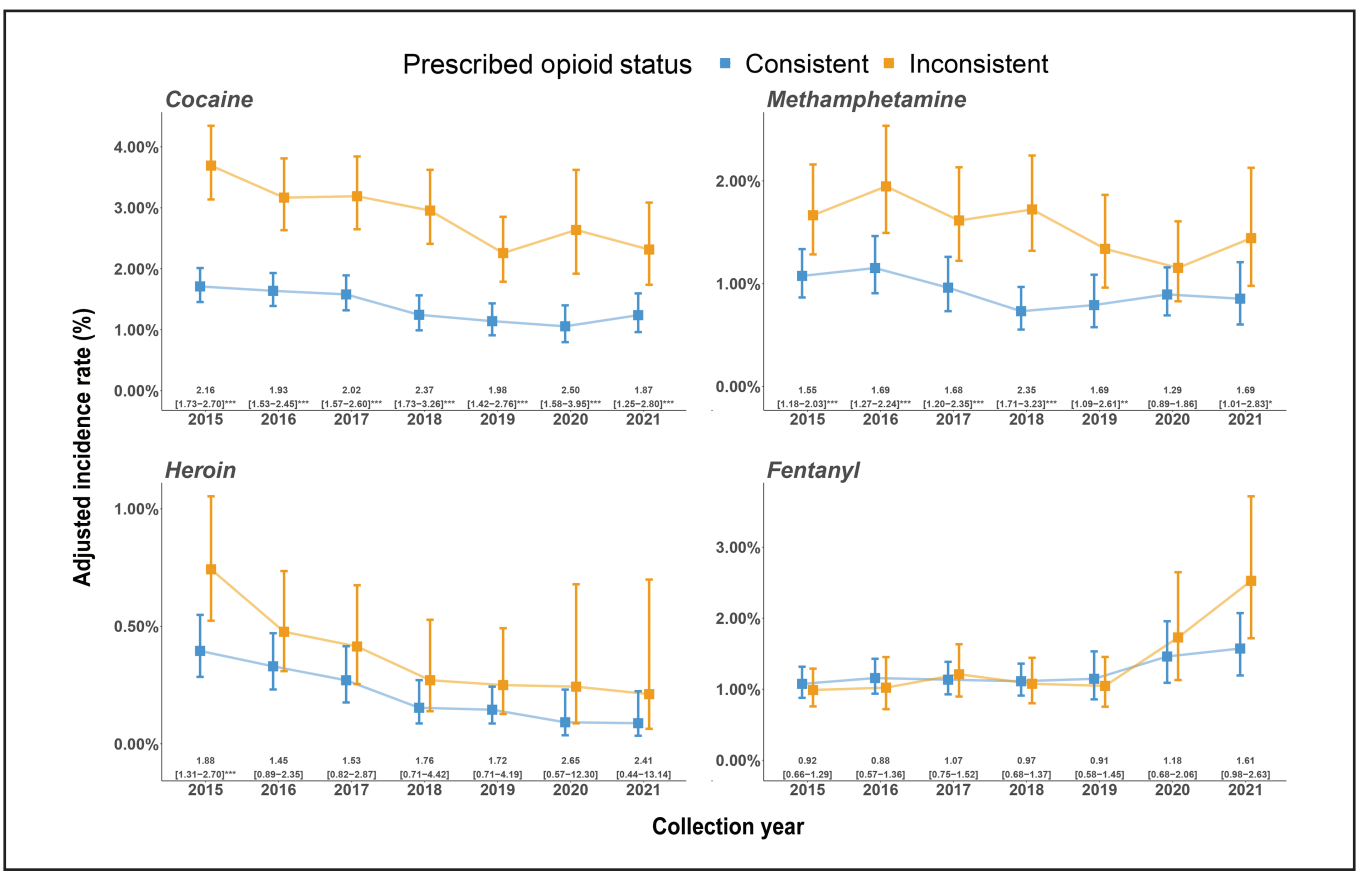

Figure 3. Yearly adjusted incidence rate of nonprescribed and illicit drugs by consistent and inconsistent prescribed opioid status.

Table 3. Yearly adjusted incidence rate ratios† (aIRR [95 percent CI]) comparing consistent and inconsistent opioid status

Collection year	Fentanyl	Heroin	Methamphetamine	Cocaine
2015	0.92 [0.66-1.29]	1.88 [1.31-2.70]***	1.55 [1.18-2.03]***	2.16 [1.73-2.70]***
2016	0.88 [0.57-1.36]	1.45 [0.89-2.35]	1.69 [1.27-2.24]***	1.93 [1.53-2.45]***
2017	1.07 [0.75-1.52]	1.53 [0.82-2.87]	1.68 [1.20-2.35]***	2.02 [1.57-2.60]***
2018	0.97 [0.68-1.37]	1.76 [0.71-4.42]	2.35 [1.71-3.23]***	2.37 [1.73-3.26]***
2019	0.91 [0.58-1.45]	1.72 [0.71-4.19]	1.69 [1.09-2.61]**	1.98 [1.42-2.76]***
2020	1.18 [0.68-2.06]	2.65 [0.57-12.30]	1.29 [0.89-1.86]	2.50 [1.58-3.95]***
2021‡	1.61 [0.98-2.63]	2.41 [0.44-13.14]	1.69 [1.01-2.83]*	1.87 [1.25-2.80]***

†aIRR represents the ratio of inconsistent/consistent incidence rates.
‡2021 data extend through September 30, 2021.
p value designation: *<0.05, **<0.01, and ***<0.001.

COVID-19 pandemic evaluation

Since our previous work showed an increase in illicit drug use in a population with SUD when comparing a prepandemic timeframe to a COVID-19 timeframe, we wanted to evaluate the potential influence of the COVID-19 pandemic on these results.[22] To determine if there was an increase in nonprescribed and/or illicit drug use after the COVID-19 emergency declaration in 2020, we evaluated additional regression models. These models compared UDT detection for samples collected between March 13, 2019 and March 12, 2020 (pre-COVID-19 timeframe) to those collected between March 13, 2020 and March 12, 2021 (COVID-19 timeframe). The inconsistent group was 50 percent more likely (IRR = 1.50, $p < 0.05$) to be positive for nonprescribed fentanyl during COVID-19 versus the pre-COVID-19 timeframe. There were no significant differences in positivity rates in the consistent group between the two timeframes or for the other nonprescribed and/or illicit drugs (Appendix Table 1).

DISCUSSION

Clinically, the results of this study may be encouraging to a clinician prescribing opioids and utilizing definitive UDT. Less than 5 percent of the total population of patients treated for pain were positive for cocaine, heroin, fentanyl, or methamphetamine, which suggests that this population may be at lower risk of use for these illicit drugs. Patients testing positive for their prescribed opioid, eg, consistent with therapy, were generally less likely to be positive for the illicit drugs included in the analysis. Compared to patients with samples found to be inconsistent, patients with samples that were found to be consistent were 54 percent less likely to be positive for cocaine, 47 percent less likely to be positive for heroin, and 35 percent less likely to be positive for methamphetamine. Given the differences observed between these groups, if a patient tests negative for their prescribed opioid on definitive UDT, a conversation about medication therapy and additional substance use may be warranted. Since the patient may be more likely to be positive for a nonprescribed or illicit substance, the clinician may also consider expanding drug testing to evaluate use of other substances, and other risk mitigation strategies.

There was no difference between the consistent and inconsistent group for illicit fentanyl, which may be due to several factors. Overall, both consistent and inconsistent groups had very low positivity rates for illicit fentanyl (1.17 and 1.96 percent in 2021, respectively). This finding is notable because, as discussed in the introduction, IMF and methamphetamine are now the primary drivers of drug overdose deaths.[6-8] It is possible that this population is aware of the dangers associated with illicit fentanyl and may be less likely to use it. Alternatively, if a patient attempts to acquire prescription opioids outside of the patient–clinician relationship, such as via

Table 4. Adjusted incidence rate ratios [95 percent CI] for additive model covariates†

Coefficients	Cocaine	Fentanyl	Heroin	Methamphetamine
Intercept	0.04 [0.03-0.06]***	0.01 [0.01-0.01]***	0.01 [0.01-0.02]***	0.01 [0.00-0.01]***
Sex				
Female (reference)				
Male	1.71 [1.60-1.83]***	1.08 [1.00-1.17]	2.02 [1.76-2.32]***	1.38 [1.28-1.49]***
Age				
18-24 (reference)				
25-34	0.96 [0.75-1.23]	1.27 [0.85-1.91]	1.07 [0.66-1.72]	1.18 [0.81-1.73]
35-44	0.90 [0.71-1.14]	1.18 [0.80-1.76]	0.61 [0.38-0.98]*	1.26 [0.87-1.84]
45-54	1.05 [0.83-1.32]	0.89 [0.60-1.32]	0.41 [0.25-0.65]***	1.31 [0.90-1.90]
55+	0.60 [0.48-0.76]***	0.60 [0.41-0.90]*	0.18 [0.11-0.29]***	0.68 [0.47-0.98]*
US census division				
East North Central (reference)				
East South Central	0.69 [0.59-0.79]***	0.73 [0.59-0.90]**	0.39 [0.24-0.61]***	3.34 [2.79-4.01]***
Mid Atlantic	1.26 [1.12-1.41]***	1.20 [1.02-1.41]*	1.62 [1.31-2.01]***	1.68 [1.34-2.10]***
Mountain	0.46 [0.41-0.52]***	1.22 [1.06-1.39]**	1.16 [0.96-1.42]	4.73 [4.14-5.41]***
New England	1.08 [0.92-1.28]	2.01 [1.62-2.49]***	1.53 [1.09-2.16]*	0.26 [0.11-0.62]**
Pacific	0.64 [0.57-0.72]***	1.22 [1.04-1.43]*	0.87 [0.66-1.16]	5.06 [4.38-5.83]***
South Atlantic	1.13 [1.03-1.25]**	1.13 [0.99-1.29]	0.84 [0.67-1.05]	1.97 [1.68-2.30]***
West North Central	0.28 [0.19-0.43]***	0.69 [0.48-0.97]*	0.10 [0.03-0.37]***	4.88 [3.73-6.40]***
West South Central	0.67 [0.59-0.78]***	0.73 [0.62-0.86]***	0.32 [0.21-0.47]***	2.98 [2.52-3.53]***
Collection year				
2015 (reference)				
2016	0.86 [0.75-0.99]*	1.03 [0.78-1.36]	0.64 [0.49-0.85]**	1.17 [0.97-1.40]
2017	0.86 [0.75-0.99]*	1.22 [0.96-1.56]	0.56 [0.40-0.77]***	0.97 [0.80-1.18]
2018	0.80 [0.69-0.93]**	1.09 [0.86-1.38]	0.36 [0.23-0.57]***	1.03 [0.86-1.24]
2019	0.61 [0.52-0.73]***	1.06 [0.82-1.37]	0.34 [0.21-0.53]***	0.80 [0.64-1.01]
2020	0.71 [0.57-0.89]**	1.75 [1.27-2.41]***	0.33 [0.16-0.65]**	0.69 [0.55-0.87]**
2021‡	0.63 [0.51-0.77]***	2.56 [1.91-3.43]***	0.28 [0.13-0.64]**	0.87 [0.66-1.13]
Prescribed opioid status				
Consistent (reference)				
Inconsistent	1.54 [1.47-1.59]***	0.91 [0.68-1.11]	1.47 [1.34-1.57]***	1.35 [1.24-1.45]***

†aIRR estimates for sex, age, US census division, collection year, and prescribed opioid status with robust 95 percent CI values.
‡2021 data extend through September 30, 2021.
Within collection year by prescribed opioid status interaction aIRR estimates are shown in Table 3.
p value designation: *<0.05, **<0.01, and ***<0.001; p values were not Tukey adjusted.

illicit sources, it is increasingly likely these drugs will contain fentanyl, as law enforcement confiscations of fentanyl-laced substances purported to be pharmaceutical-grade opioids have grown.[27] A patient may choose to seek prescription opioids from nonmedical sources for a variety of reasons, including lack of access due to clinician fear of regulatory scrutiny, inefficacy of their prescribed medication, diversion, or potential SUD. Previous work has also shown high rates of UDT co-positivity of illicit fentanyl with other drugs, with one report showing 92 percent of heroin-positive specimens, 41 percent of methamphetamine-positive specimens, and 36 percent of cocaine-positive specimens also contained fentanyl.[28] At-risk patient populations would likely benefit from education about the hazards associated with the infiltration of fentanyl into the illicit drug supply and the inherent danger it presents, particularly in counterfeit form, which may appear identical to pharmaceutical-grade products. Additionally, when monitoring with UDT, finding fentanyl with a prescription opioid may indicate that a patient is obtaining an opioid from a nonmedical source.

The majority of samples (76 percent) from those prescribed opioids were found to be consistent with prescribed medication, and less than 5 percent of the total population had an illicit drug present. It is difficult to make direct comparisons of this 76 percent rate to those reported historically in other studies due to different methods, eg, presumptive instead of definitive testing and populations. That said, this rate does compare quite favorably with at least one similar study from 15 years ago. In 2007, Michna et al. published a characterization of a cohort of patients (N = 470) prescribed opioids in a pain management setting via UDT using gas chromatography-mass spectrometry (GC/MS), and the detection of prescribed hydrocodone, fentanyl, morphine, and oxycodone ranged from 25.7 to 81.8 percent. About 20 percent of their cohort was found to have an illicit substance present; however, the authors included additional drugs, such as marijuana, in their analysis.[29] Current opioid prescribing has been cut to almost half of what it was previously, potentially resulting in more careful selection of patients prescribed opioids. Using UDT as part of monitoring has been shown in other populations to improve the patient–clinician therapeutic relationship.[30] Our study population may represent a sample of patients who were more consistently monitored with UDT than other populations of patients with pain, potentially contributing to improved medication-taking behavior. Additionally, we only chose to examine four illicit substances known to contribute to drug overdose deaths; other drugs known to increase the likelihood of overdose, including benzodiazepines and alcohol as well as other central nervous system depressants, may play an important role in unintended overdose fatalities in a patient prescribed opioid therapy.[31]

It must be noted, however, that 24 percent of the population prescribed opioids were negative (inconsistent) for their prescribed opioid, and those negative were more likely to be positive for an illicit substance. Unexpected UDT results, particularly a prescribed medication that is absent on definitive UDT, may be due to several factors which should be explored, including timing of medication use, as-needed medication use, drug interactions, pharmacogenetic considerations, misuse, and diversion. Like any other objective lab measurement, UDT results must be placed in the clinical context of the patient's presentation. Additionally, if using immunoassay testing such as point-of-care cups, the results should be considered presumptive, with the possibility of false-positives or false-negative results; caution should be taken when making clinical decisions based on a presumptive UDT only.[21] When unexpected results occur, guidelines suggest the clinician may want to consider a medication change if the patient is not meeting goals of care; monitoring more closely via pill counts, PDMP, and potentially increasing frequency and/or randomization of UDT; or an evaluation for SUD with referral.[19] Even if a patient is exhibiting aberrant behaviors that require referral, it is important to remember that a clinician treating pain can offer pain management options that do not involve controlled substances and continue to support the patient. There may also be situations where coprescribing naloxone may be warranted, including patients prescribed high-dose opioid therapy or concurrent benzodiazepines, those positive for nonprescribed or illicit substances, and those with significant medical comorbidities where there is an increased risk of opioid-induced respiratory depression.[10,19] Finally, patients who are positive for illicit drugs on UDT should receive additional careful consideration and evaluation.

The population of patients with pain tested in this study had a lower overall rate of definitive UDT positivity for cocaine, nonprescribed fentanyl, heroin, and methamphetamine than in a study by Twillman et al.,[23] which included those in an

expanded population of healthcare patients, including patients in a pain management setting, as well as SUD treatment, primary care, behavioral health, and obstetrics/gynecology. That study found that in 2019, 4.94 percent were positive for cocaine, 4.72 percent were positive for nonprescribed fentanyl, 1.99 percent were positive for heroin, and 8.39 percent were positive for methamphetamine.[23] In our total population, raw positivity rates in 2019 were 1.76, 1.32, 0.25, and 2.00 percent, respectively. This finding is notable because, as discussed in the introduction, IMF and methamphetamine are now the primary drivers of drug overdose deaths.[6-8] It also suggests that the population of patients with pain may be at lower risk of use for these illicit drugs. Patients who are positive for illicit drugs on UDT should receive additional careful consideration and evaluation.

Patient samples least likely to be positive for these illicit drugs were female and aged 55 or older. Among the many factors related to individual risk of aberrant behavior are a range of demographic, psychiatric, genetic, familial, and spiritual variables.[32,33] Epidemiologically, older age and female sex are associated with lower rates of substance use.[15] We found this in the present study as well. In the end, these demographic factors should be considered alongside more individualized aspects of the patient's history to determine whether and how a trial of opioid therapy should be undertaken. If access to opioid therapy is to be widened in future versions of the CDC guidelines, these factors should be taken into account so as to raise the likelihood of safe and positive outcomes for patients undergoing opioid therapy.

Finally, in March 2020, DEA-registered practitioners were allowed to temporarily prescribe controlled substances without an in-person visit, extending the duration of the public health emergency.[34] Despite less restrictions to access as well as other factors that may have contributed to a rise in drug misuse during the pandemic, such as added stress, isolation, and worsening mental health among the general population,[35] we found only that the inconsistent group was 50 percent more likely to be positive for illicit fentanyl. Otherwise, we saw no significant differences between the groups when comparing the pre-COVID-19 timeframe to the COVID-19 timeframe. Careful patient selection, assessment, and appropriate monitoring of people with pain undergoing opioid therapy may help patients to continue to have positive outcomes even when stressful situations might have otherwise been expected to expose and worsen vulnerabilities that could have led to drug misuse.

As experts work to update guidelines for prescribing of opioids with the possibility of greater access and flexibility being debated, decision-making should be based on current patterns of drug use in populations of patients with pain. To this end, aggregated, definitive UDT data can be used as a data stream to quickly identify and track drug use trends.

CONCLUSIONS

In this study, overall positivity rates for cocaine, heroin, fentanyl, and methamphetamine were low. Patients consistent on UDT with opioid therapy were less likely to be positive for cocaine, heroin, or methamphetamine. Unlike in a SUD population, there were almost no differences when comparing the groups from the pre-COVID-19 timeframe to the COVID-19 timeframe. These findings show the capability of UDT to evaluate drug use trends in a pain management population, and the capacity of UDT to contribute to tracking drug use trends among individual healthcare populations and evaluate factors influencing positivity of prescribed and illicit substances. As access to prescription opioids continues to be in flux, current data, including the findings presented here, characterizing patients prescribed opioids should be used to inform ongoing policy and prescribing decisions. It also continues to remain clear that clinicians will need to approach opioid therapy with an appropriate level of caution considering what has been learned from the events of the last two decades and will need to utilize and document careful monitoring, including with UDT and other tools, to help prevent another rise in misuse, diversion, overdose, and death.

LIMITATIONS

This study has several limitations. Data are limited to a population of patients prescribed opioids in a pain management setting and may not be generalizable to patients prescribed opioids in other settings, such as primary care. The practice specialty categorization, ie, pain management specialty practice, was initially chosen by Millennium Health and subsequently verified by the ordering clinician. Practices may have overlap or include patients in other types of healthcare populations. Individuals included in

the analysis may have had an incomplete or inaccurate medication list. Additionally, we were unable to verify if reported prescriptions were ultimately dispensed to the patient; some patients may have received an opioid prescription they did not fill. The five prescribed drugs were not equally distributed in the population; therefore, the power to detect differences was not equivalent. We categorized patients into the consistent group even if they only had one prescribed opioid found in the urine. We were unable to evaluate copositivity for illicit fentanyl in those prescribed fentanyl (<3 percent of the population evaluated). As with any UDT method used, our test was unable to differentiate the source of morphine, eg, from prescribed medication versus heroin as well as the source of fentanyl, eg, prescribed pharmaceutical-grade fentanyl versus IMF; however, we attempted to address this by removing specimens with reported prescriptions for fentanyl in the stratification evaluating illicit and nonprescribed drug use. We chose to focus the analysis on copositivity for the most common substances involved in drug overdose deaths, especially in combination with prescribed opioids; however, we did not use an all-inclusive list of psychoactive substances, and future analysis may be warranted. In using the first UDT specimen during the timeframe evaluated for each patient, it is unknown at which point in the spectrum of care the patient is in, eg, early on in opioid initiation, new to a practice, or in the regular course of pain management care with a new lab in place. In practice, some patients may first be screened with a presumptive, eg, in-office, test performed with immunoassay technology; study findings may not be generalizable to patients who receive only presumptive tests, considering immunoassays may show cross-reactivity with other substances and have higher cutoffs, which may result in false negatives. Additionally, it should be remembered that synthetic opioids, such as fentanyl, are not readily detected with an in-office presumptive test.[36]

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Appendix Table 1. Adjusted incidence rate ratios[†] (aIRR [95 percent CI]) comparing the pre-COVID-19[‡] to COVID-19[§] time periods stratified by prescribed opioid status

Contrast	Cocaine	Fentanyl	Heroin	Methamphetamine
Inconsistent	1.16 [0.82-1.63]	1.50 [1.00-2.24]*	0.68 [0.16-2.86]	1.02 [0.73-1.42]
Consistent	0.98 [0.73-1.33]	1.24 [0.94-1.63]	1.21 [0.54-2.71]	0.99 [0.77-1.27]

[†]aIRR represents the ratio of COVID-19/pre-COVID-19 incidence rates.
[‡]The pre-COVID-19 time period extends from March 13, 2019 to March 12, 2020.
[§]The COVID-19 time period extends from March 13, 2020 to March 12, 2021.
p value designation: *<0.05.