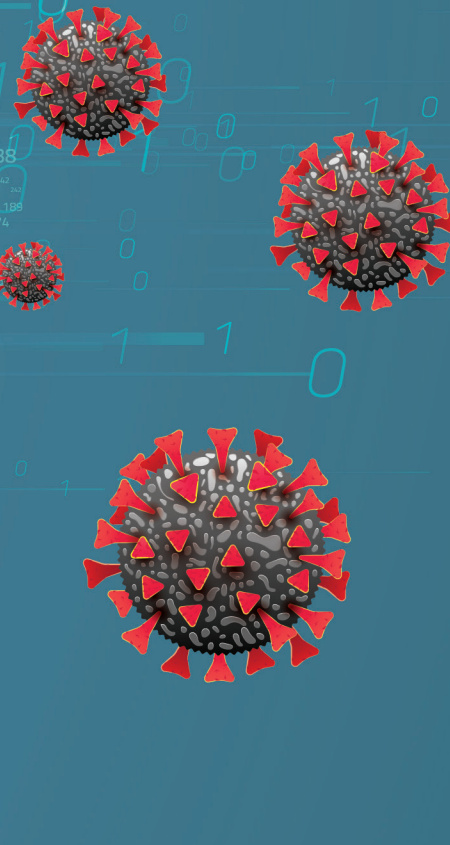



Millennium Health Signals Report™

The COVID-19 Connection: Tracking 2020 Trends in Drug Use

Volume 3

Published February 2021





Millennium Health is an accredited specialty laboratory with over a decade of experience in drug testing services allowing clinicians to monitor the use of prescription medications and illicit drugs and effectiveness of treatment plans. Processing over a million specimens each year allows us to provide real-time analytics regarding emerging drug use trends.

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Foreword



Andrew A. Lukowiak, PhD
Chief Executive Officer,
Millennium Health



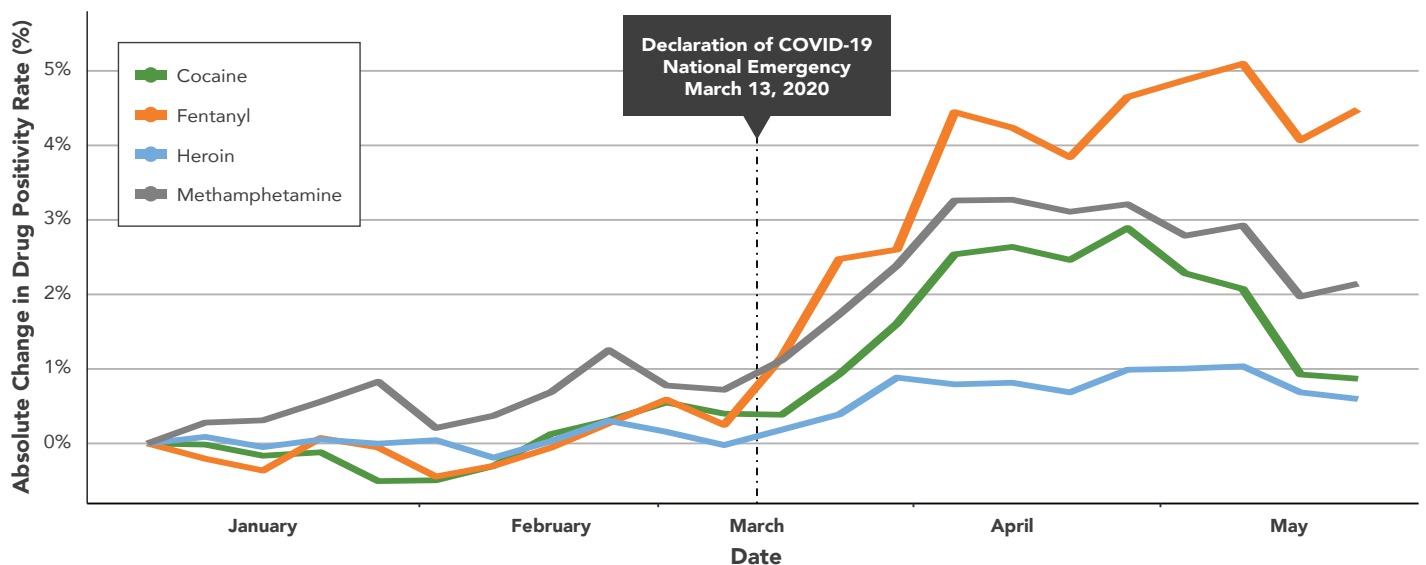
Angela G. Huskey, PharmD, CPE
Chief Clinical Officer,
Millennium Health

This past year has presented unprecedented challenges due to the novel coronavirus disease 2019 (COVID-19) pandemic. Approximately 80% of adults identify the pandemic as a significant source of stress, and nearly 20% report worsening mental health.¹ Certain populations, including those with substance use disorders (SUD), have been disproportionately affected, with not only risk of relapse, but increased risk of contracting the virus.² Patients with SUD who are diagnosed with COVID-19 face significantly higher rates of hospitalization and death than the general population.² In addition to mounting deaths related to the virus itself, the nation is also experiencing “a concerning acceleration of the increase in drug overdose deaths.”³ Early indicators suggest that the United States is on track to record a new all-time high for overdose deaths in 2020.⁴

Amidst these unfortunate, evolving circumstances, Millennium Health remains committed to reporting on drug use trends during the pandemic to identify areas where clinicians and public health officials can focus treatment and prevention efforts. In July 2020, we released a COVID-19 Special Edition of the Millennium Health Signals Report™ demonstrating significant increases in drug positivity between March and May 2020 compared to the pre-COVID-19 time period (Figure 1).⁵ In December, data from the CDC paralleled our findings, reporting that overdose deaths recorded between March and May had the largest monthly increases documented since provisional estimates began to be calculated.³

We followed our COVID-19 Special Edition Signals Report with a peer-reviewed publication in *JAMA*, co-authored with the U.S. Department of Health

Figure 1. Total Study Population Change in Unadjusted Positivity Rate for Cocaine, Fentanyl, Heroin and Methamphetamine



and Human Services.⁶ This *JAMA* Research Letter expanded the timeframe of our Signals analysis and identified a sustained increase in the likelihood of testing positive for non-prescribed fentanyl, cocaine, heroin, and methamphetamine during the COVID-19 time period. We have continued to analyze our data throughout the pandemic to keep those fighting the overdose crisis informed with the very latest trends. Our latest findings are presented in Section 1 of this report.

In 2020, Millennium Health researchers also published a study⁷ in *Drug and Alcohol Dependence* examining the frequency of fentanyl and several fentanyl analogues in definitive urine drug tests (UDT) collected prior to the March 13, 2020 declaration of a national emergency concerning the COVID-19 outbreak.⁸ In Section 2 of this report, we investigate the potential impact COVID-19-related changes have had on fentanyl analogue positivity.⁹

March 2020 also brought about new prescribing regulations. DEA-registered practitioners may prescribe controlled substances without in-person interactions with patients for the duration of the public health emergency.¹⁰ While rates of misuse and overdose deaths associated with prescription opioids have declined in recent years,^{11,12} concerns about these risks remain, which led us to evaluate potential misuse of commonly prescribed pain medications in Section 3.

Lastly, in Section 4, we focus on methadone. In March 2020, the Substance Abuse and Mental Health Services Administration (SAMHSA) recognized the evolving needs of patients that are part of opioid treatment programs.¹³ Because

of challenges in obtaining medications during the pandemic, state and federal agencies eased restrictions on take-home methadone doses for stable patients.¹⁴ While these changes have led to increased accessibility, there are questions about what this availability may mean, particularly in light of increasing risks of relapse and overdose in 2020.^{2,3}

In summary, this volume of the Millennium Health Signals Report focuses on trends in positivity through 2020 for the following topics:

- 1. Non-prescribed fentanyl, cocaine, heroin, and methamphetamine**
- 2. Fentanyl analogues**
- 3. Medications commonly prescribed for pain**
- 4. Methadone and select non-prescribed and illicit substances**

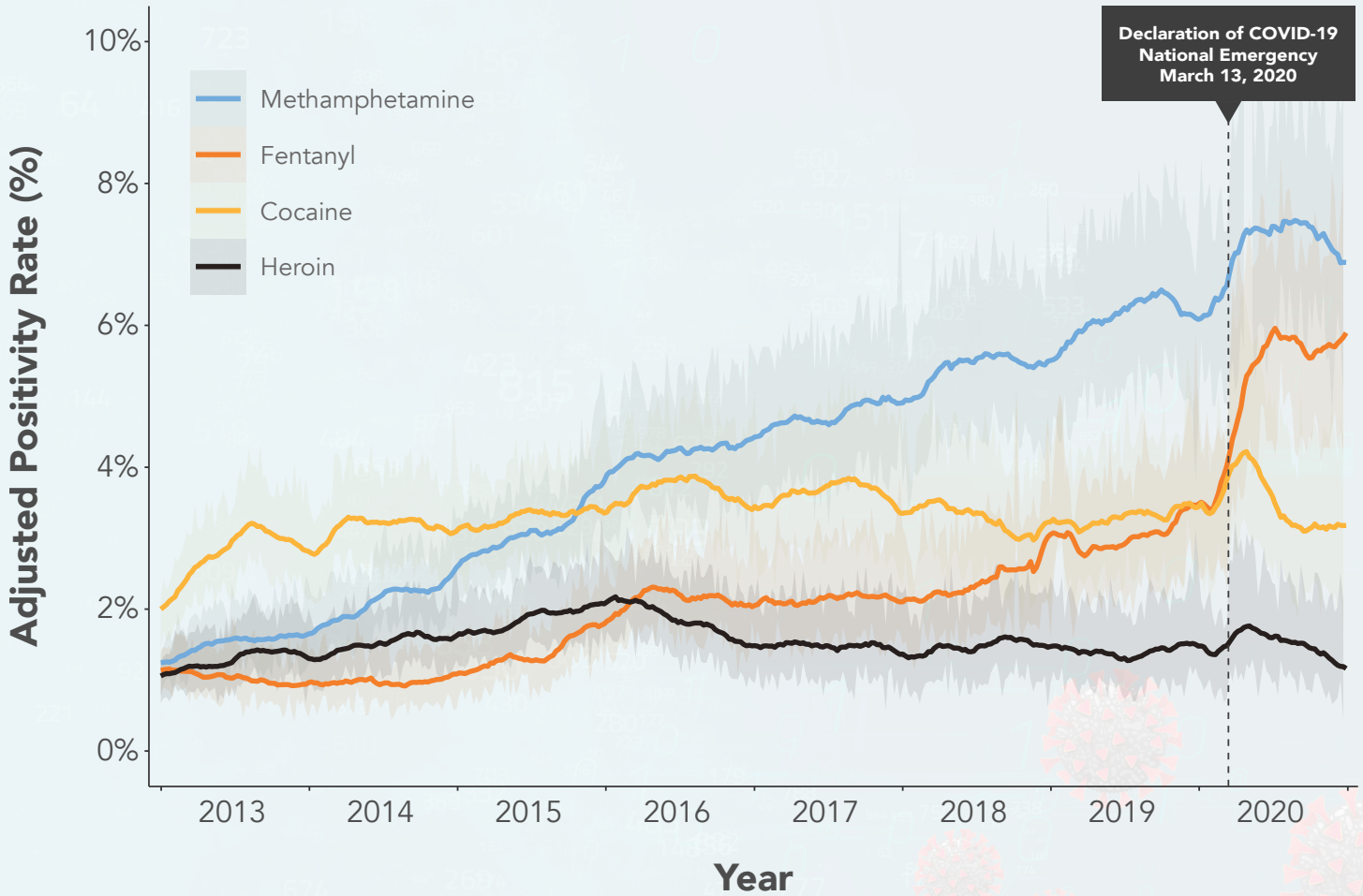
We conclude this report with commentary from Dr. Michael Parr, a board-certified physician in addiction medicine, who is dedicated to helping those with SUD. Dr. Parr summarizes the challenges faced by patients, clinicians, and public health officials in these extraordinary times and emphasizes the important role that data can play in identifying emerging substance use trends.

We thank you for your interest in our Millennium Health Signals Report and affirm our commitment to sharing this important research and continuing our collaborative efforts with clinicians, policy makers, and public health agencies in an effort to positively impact the lives of patients, their families, and communities. ●

Section 1

Shifts in Illicit Drug Use Heighten the COVID-19 Health Crisis

Figure 1. UDT Drug Positivity Rates



Adjusted positivity rates and 95% CI values for cocaine, methamphetamine, heroin, and fentanyl were estimated for each week between January 1, 2013 and December 31, 2020. Rates were adjusted for age, sex, U.S. census division, and specialty of the referring clinic using Poisson regression. A 12-week moving average of the adjusted positivity rates is shown as a thick line. The vertical dashed line reflects the U.S. national emergency declaration on March 13, 2020.

Background

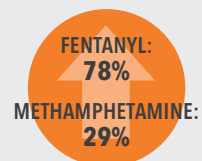
Early indicators suggest that the United States is on track to record a new all-time high for overdose deaths in 2020.⁴ The majority of these overdose deaths are attributed to use of illicit fentanyl,¹² though stimulant-involved overdose deaths are also increasing, often in combination with opioids, such as heroin or fentanyl.^{12,15}

In 2019, methamphetamine was the most frequently identified drug confiscated by law enforcement followed by cannabis, cocaine, heroin, and fentanyl.¹⁶ Because these substances are widely available and contribute significantly to overdose deaths, Millennium Health researchers have closely tracked trends in urine drug test (UDT) positivity for these substances.^{6,17-19}

In a COVID-19 Special Edition of the Millennium Health Signals Report published in July 2020,⁵ and subsequent *JAMA* publication co-authored with the U.S. Department of Health and Human Services,⁶ findings revealed that compared with the period before COVID-19 was declared a national emergency, the population tested during COVID-19 were more likely to test positive for non-prescribed fentanyl, cocaine, heroin, and methamphetamine. This initial research was conducted through July 10, 2020. Because drug use likely continued to evolve during the pandemic, this section presents a prolonged analysis of the data, extending an additional six months through December 31, 2020.

Key Findings

In this section, we evaluated adjusted UDT positivity rates for non-prescribed fentanyl, methamphetamine, heroin, and cocaine comparing pre-COVID-19 (March 13, 2019 – December 31, 2019) and COVID-19 (March 13, 2020 – December 31, 2020) time periods. Findings include:



Nationally, adjusted UDT positivity **increased significantly** during COVID-19 for **fentanyl** and **methamphetamine**, increasing 78% and 29%, respectively. After initially increasing, cocaine and heroin appear to have fallen below March 13, 2020 levels (Figure 1, Table 1)



All U.S. census divisions had a significant increase in positivity rate for at least one of the drugs evaluated (Table 1). Notably, the East North Central and Mountain divisions had significant positivity rate increases for three of the four drugs (Table 1)



Fentanyl increased significantly in all census divisions, led by increases in the Pacific division. Four Pacific states (**Washington, Oregon, Alaska, and California**) more than **doubled** their fentanyl positivity during COVID-19



Methamphetamine increases were led by the **New England division**, followed by the **Mid Atlantic**



Fifteen states had statistically significant increases in positivity rates for at least one of the drugs evaluated. **Arizona** showed increases in three drugs (Table 2)

Shifts in Illicit Drug Use Heighten the COVID-19 Health Crisis (continued)

Table 1: Positivity Rate Change for U.S. Census Divisions between the Pre-COVID-19 and COVID-19 Time Periods[†]

U.S. Census Division	Fentanyl	Methamphetamine	Heroin	Cocaine
East North Central	75% [61 - 89]*	33% [21 - 46]*	18% [-3 - 43]	12% [3 - 23]*
East South Central	34% [19 - 51]*	12% [1 - 24]	1% [-22 - 32]	-11% [-26 - 7]
Mid Atlantic	117% [52 - 209]*	59% [10 - 132]*	25% [-41 - 164]	28% [-3 - 68]
Mountain	125% [93 - 161]*	39% [26 - 53]*	36% [10 - 66]*	1% [-17 - 23]
New England	82% [29 - 157]*	119% [35 - 258]*	20% [-64 - 301]	24% [-15 - 81]
Pacific	180% [129 - 243]*	-2% [-10 - 6]	16% [0 - 34]	-9% [-27 - 14]
South Atlantic	26% [7 - 49]*	18% [0 - 39]	-37% [-57 - -9]*	-18% [-29 - -5]*
West North Central	58% [24 - 101]*	-3% [-15 - 11]	-7% [-39 - 43]	-28% [-48 - -1]
West South Central	57% [8 - 128]*	19% [-1 - 42]	31% [-25 - 129]	-6% [-29 - 24]
U.S. Total	78% [70 - 87]*	29% [23 - 35]*	9% [-2 - 21]	-2% [-7 - 3]

-40%	0%	+200%
Change in Positivity Rate		

* p<0.01

† Adjusted positivity rates change [95% CI] for the Pre-COVID-19 (March 13, 2019 - December 31, 2019) and the COVID-19 (March 13, 2020 - December 31, 2020) time periods

Table 2: Positivity Rate Increases* by State between the Pre-COVID-19 and COVID-19 Time Periods[†]

Fentanyl		Methamphetamine		Heroin	
Washington	236% [126 - 399]	Virginia	336% [114 - 789]	Nevada	600% [32 - 3612]
Alaska	220% [52 - 575]	Nevada	324% [133 - 672]	Arizona	88% [25 - 183]
Arizona	170% [116 - 236]	Maine	152% [18 - 440]		
Mississippi	166% [20 - 487]	New York	104% [13 - 267]		
Maine	165% [48 - 373]	Arizona	77% [45 - 115]		
North Carolina	161% [39 - 391]	Ohio	30% [15 - 47]		
Missouri	159% [47 - 357]				
California	146% [60 - 279]				
Michigan	145% [34 - 347]				
New York	133% [36 - 298]				
Oregon	115% [12 - 311]				
Ohio	68% [52 - 86]				
Kentucky	25% [8 - 45]				

* p<0.01

† Adjusted positivity rates change [95% CI] for the Pre-COVID-19 (March 13, 2019 - December 31, 2019) and the COVID-19 (March 13, 2020 - December 31, 2020) time periods

No statistically significant changes were noted for cocaine at the state level

Conclusions

These findings, particularly those indicating a sustained rise in fentanyl and methamphetamine positivity, are concerning due to their harmful health consequences and notable contributions to drug overdose deaths. While fentanyl positivity grew the most in the Pacific and Mountain divisions during

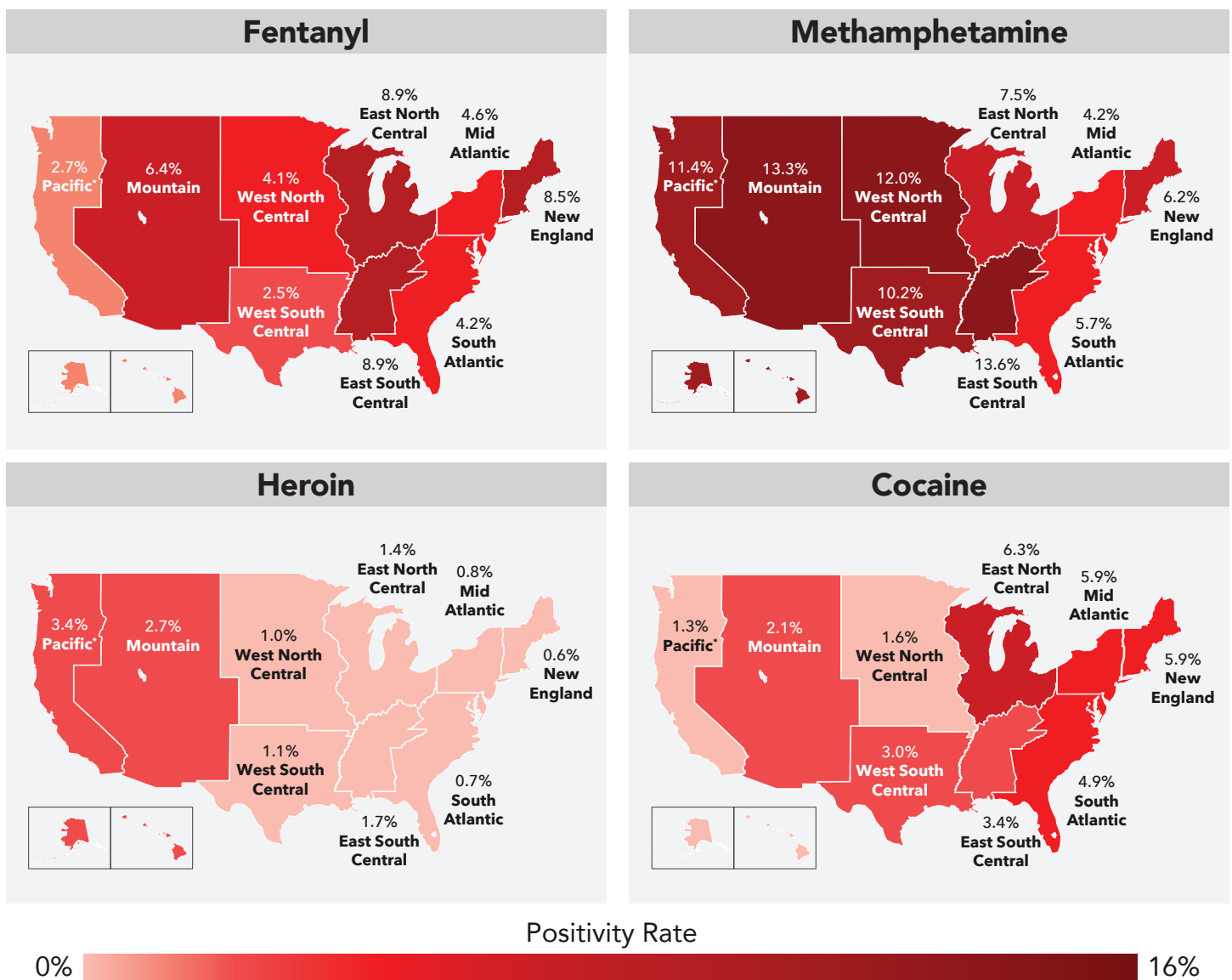
COVID-19, overall positivity rates are highest in the East North Central and East South Central divisions (Figure 2). The remarkable increase in fentanyl positivity in the West coincides with a large increase in synthetic opioid-related deaths noted for this region by the CDC.³

Deaths involving psychostimulants, including methamphetamine, have also increased both with and without co-use of synthetic opioids and now exceed those involving cocaine.³ While methamphetamine positivity rates are highest throughout the West and Midwest (Figure 2), use is growing in nontraditional markets, including the Northeast, as evidenced by significant increases in the New England and Mid Atlantic divisions.¹⁹ Methamphetamine use poses unique challenges because there is no antidote for methamphetamine overdose and no FDA-approved medications

indicated for the treatment of methamphetamine use disorder.¹⁹ Continued research and strategies to improve treatment and prevention efforts are needed to address these health consequences.

Substance use trends are dynamic and will likely continue to evolve as the nation continues to cope with the devastating impact COVID-19 has had on communities. Having access to national, regional, and state-level data, including UDT, will be important to continue observing trends over time. ●

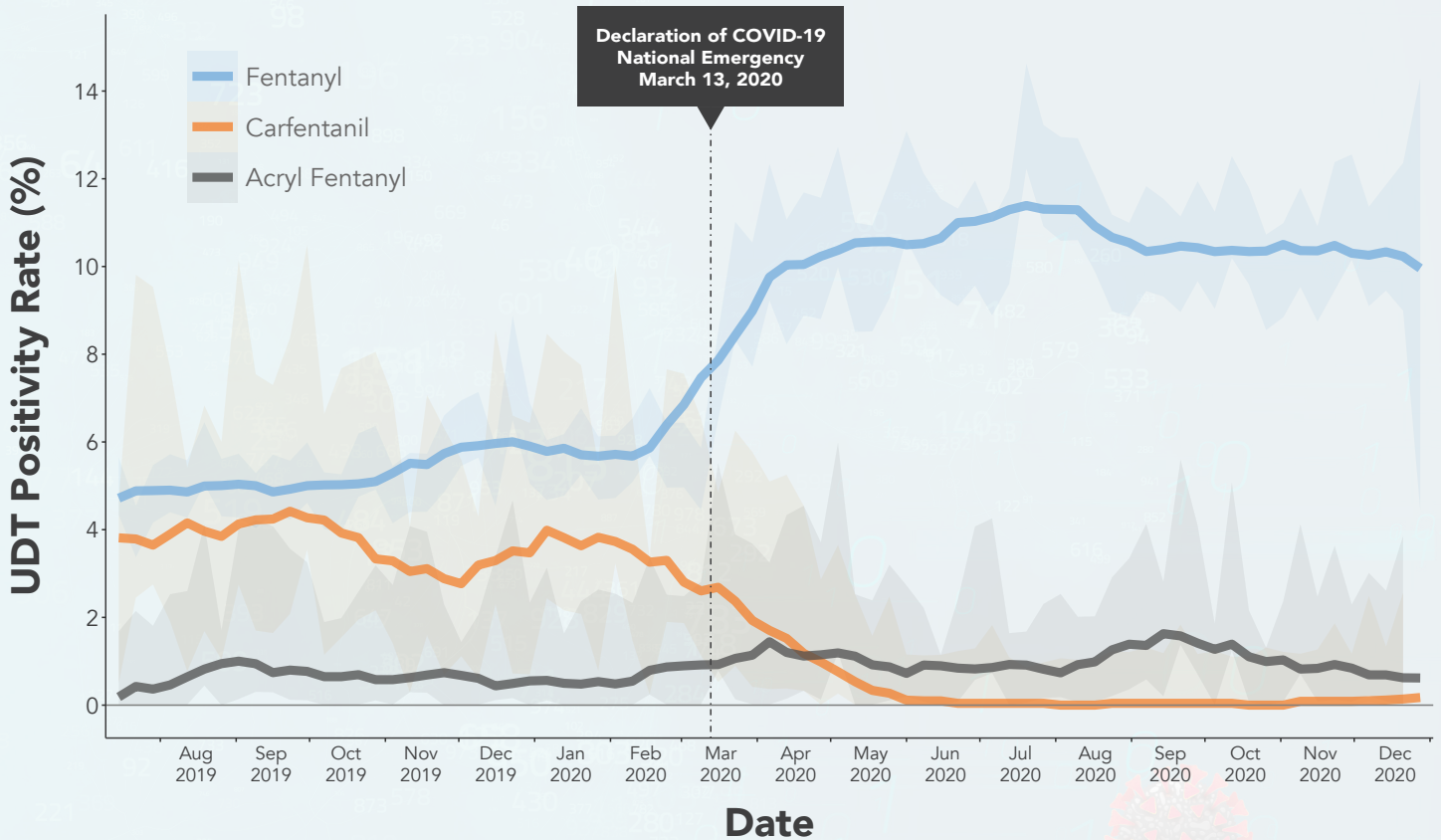
Figure 2. Adjusted Positivity Rates (%) for U.S. Census Divisions During the COVID-19 Time Period (March 13, 2020 - December 31, 2020)



Section 2

The Collapse of Carfentanil

Figure 1. Fentanyl and Fentanyl Analogue Positivity Rates Between July 15, 2019, and December 31, 2020



Positivity rates [95% CI] for fentanyl, carfentanil, and acryl fentanyl are shown for each week. A rolling 4-week average is also shown. Fentanyl positivity was calculated for the entire population. Fentanyl analogue positivity was only calculated for the fentanyl-positive population due to the reflex testing method used in the analysis (described in Methods).

Background

Fentanyl analogues are chemicals that are structurally similar to fentanyl, but slightly altered. They range in potency and U.S. distribution.⁷ The most potent analogue, carfentanil, is up to 10,000 times more potent than morphine and 100 times more potent than fentanyl. Fentanyl analogues, especially carfentanil, pose a serious risk for overdose, as evidenced by the contribution of synthetic opioids, including illicit fentanyl and its analogues, to over half of drug overdose deaths.^{12,20}

A recent study by Stanton et al.⁷ examined the frequency of UDT positivity for fentanyl and eleven fentanyl analogues between July 15, 2019, and March 12, 2020. In this study, carfentanil was detected in 3.13% of all specimens from patients positive for fentanyl without a prescription, with the top 10 counties all located in northeastern Ohio; the second most commonly identified analogue not associated with fentanyl metabolism or synthesis was acryl fentanyl. Other analogue findings were rare.⁷ Therefore, we focused this analysis on fentanyl, carfentanil, and acryl fentanyl.

Key Findings

In this section, we analyzed 250,000 unique patient specimens collected between July 15, 2019, and December 31, 2020. Findings include:



Carfentanil detection dropped sharply after the COVID-19 declaration, decreasing from 3.7% [3.2-4.1] before March 13, 2020 to 0.3% [0.2-0.4]



While 95% of carfentanil findings in this period were located in Ohio, **acryl fentanyl was identified in 18 states**, led by **Ohio, Kentucky, and Arizona**



Carfentanil's near disappearance leaves **acryl fentanyl as the most commonly identified fentanyl analogue** (Figure 1)

Conclusions

In contrast to increasing UDT positivity for fentanyl, carfentanil detection dropped to nearly 0%, making acryl fentanyl the most commonly identified fentanyl analogue. Acryl fentanyl positivity is not common but is significant, as acryl fentanyl has a potency similar to fentanyl and a wider U.S. distribution than carfentanil.⁷

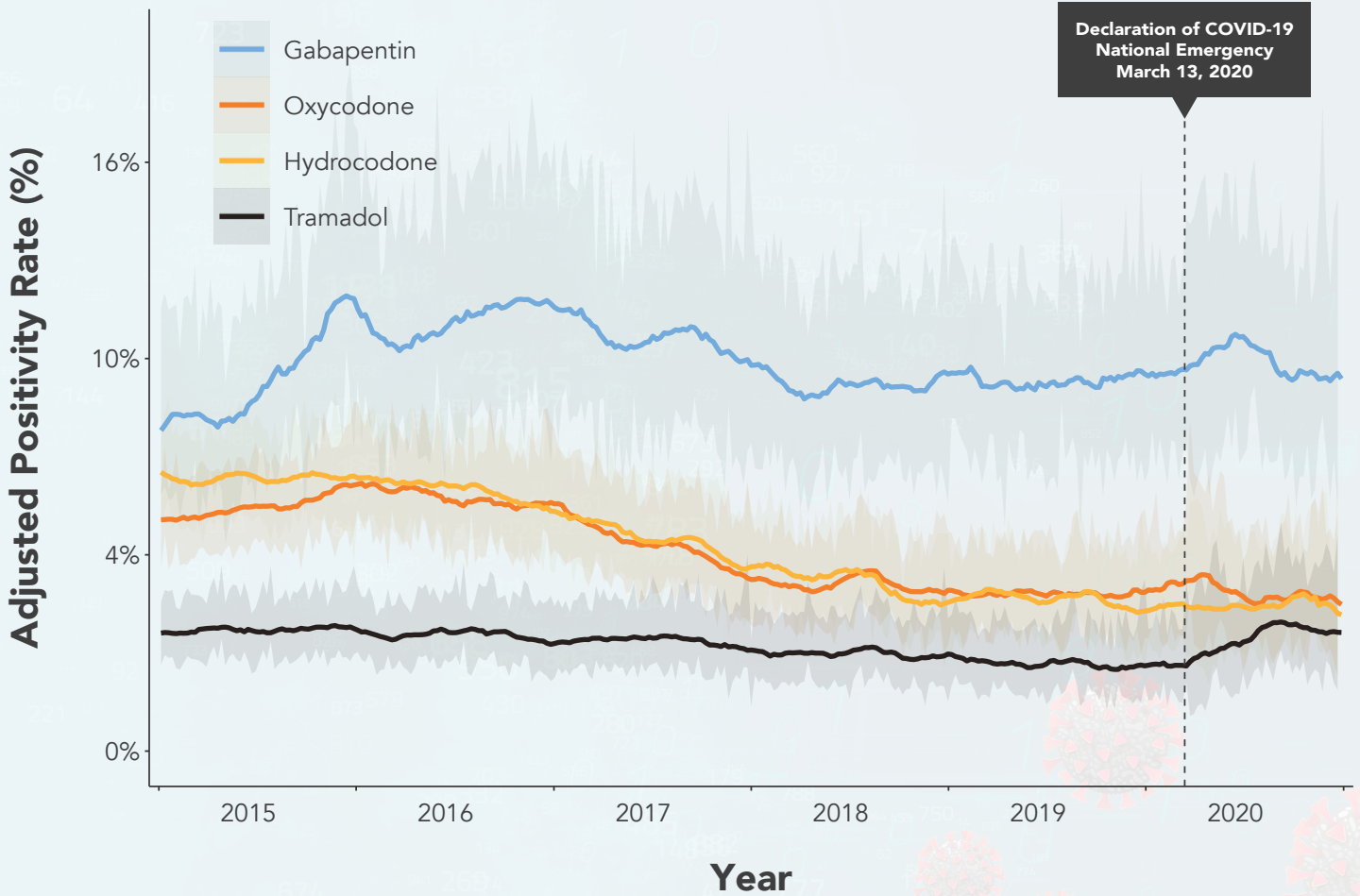
It is unclear why there was such a substantial reduction in carfentanil positivity. Possible reasons include reduced availability of precursor molecules needed for synthesis, especially those originating

from China, changes in traditional supply routes associated with international border closures, and changes in manufacturing methods and locations.⁹ User habits may have also changed due to social isolation, such as seeking substances online. The decrease in carfentanil is especially important given the association between carfentanil availability and overdose mortality.²⁰ Monitoring of this substance, along with other fentanyl analogues, can help identify whether these trends continue moving forward, as use of synthetic drugs typically fluctuate widely based on a number of factors, including availability. ●

Section 3

An Evaluation of Pain Medication Misuse in the Midst of the Pandemic

Figure 1. UDT Positivity Rates for Non-Prescribed Medications



Adjusted positivity rates and 95% CI values for gabapentin, tramadol, oxycodone, and hydrocodone were estimated for each week between January 1, 2013 and December 31, 2020 (data before 2015 not shown). Patients with reported prescriptions for any of these medications were excluded. Rates were adjusted for age, sex, U.S. census division and specialty of the referring clinic using Poisson regression. A 12-week moving average of the adjusted positivity rates is shown as a thick line. The vertical dashed line reflects the U.S. national emergency declaration on March 13, 2020.

Background

The prescribing of medications used to treat pain has changed in recent years due to a number of factors. For example, in 2014, after more than thirty years as Schedule III drugs, hydrocodone combination products became more stringently controlled Schedule II drugs.²¹ Following this change, prescribing rates of lesser or non-controlled pain medications increased, including tramadol and gabapentin.^{22,23} Despite reports of tramadol misuse remaining steady,¹¹ drug confiscations by law enforcement have increased 145% since 2014, making tramadol the twelfth most frequently identified drug in 2019.^{16,24} Concerns about gabapentin misuse and diversion have also emerged. While evidence suggests that gabapentin misuse is growing, there appear to be regional differences.²⁵ Volume 1 of the Millennium Health Signals Report identified relatively stable rates of non-prescribed gabapentin among definitive UDTs collected between 2014 and 2018, at an

approximate rate of 12% nationally with some regional variability.²⁶

Effective March 2020, DEA-registered practitioners are permitted to prescribe controlled substances without in-person interactions with patients for the duration of the public health emergency, though in the case of Schedule II drugs, including oxycodone and hydrocodone, written or electronic prescriptions are still required except in emergency situations. Schedule III-V medications, including tramadol, are permitted to be called in to pharmacies.¹⁰

While rates of misuse and overdose deaths associated with prescription opioids have declined in recent years,^{11,12} some concerns about these risks remain. Professional guidelines recommend comprehensive monitoring plans for patients prescribed opioids, including monitoring via drug testing for use of prescribed, non-prescribed, and illicit substances.²⁷

Key Findings

In this section, we evaluated adjusted UDT positivity rates for non-prescribed tramadol, gabapentin, hydrocodone, and oxycodone, comparing pre-COVID-19 (March 13, 2019 - December 31, 2019) and COVID-19 (March 13, 2020 - December 31, 2020) time periods. Findings include:



Tramadol positivity increased significantly during COVID-19, largely driven by increases in the East North Central (i.e. **Ohio**) and East South Central (i.e. **Tennessee and Kentucky**) divisions (Table 1)



While **gabapentin also increased significantly**, largely due to increases in the East North Central and West South Central (Table 1), the spike in positivity seen initially during the COVID-19 time period now appears to have **decreased back to pre-COVID-19 rates** (Figure 1)

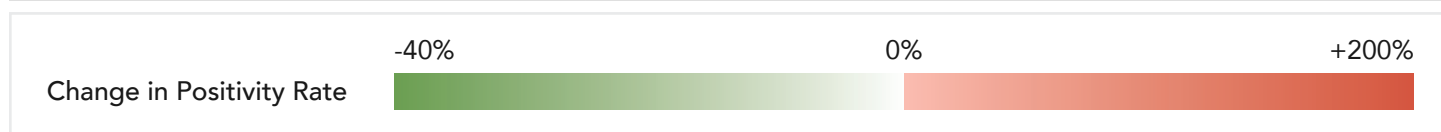


Hydrocodone and oxycodone positivity did not change significantly, with the exception of a significant decline in positivity for hydrocodone in the South Atlantic division (Table 1)

An Evaluation of Pain Medication Misuse in the Midst of the Pandemic (continued)

Table 1. Non-Prescribed Positivity Rate Change for U.S. Census Divisions between the Pre-COVID-19 and COVID-19 Time Periods[†]

U.S. Census Division	Gabapentin	Tramadol	Hydrocodone	Oxycodone
East North Central	15% [5 - 27]*	110% [78 - 148]*	2% [-16 - 23]	3% [-13 - 21]
East South Central	8% [-5 - 23]	64% [26 - 113]*	5% [-13 - 25]	-4% [-21 - 17]
Mid Atlantic	21% [-4 - 52]	27% [-12 - 84]	5% [-22 - 41]	6% [-19 - 40]
Mountain	-7% [-20 - 8]	-16% [-32 - 5]	-12% [-26 - 5]	-11% [-24 - 3]
New England	35% [-15 - 112]	66% [-12 - 212]	2% [-52 - 118]	-13% [-50 - 51]
Pacific	10% [-11 - 36]	9% [-19 - 47]	4% [-15 - 27]	-10% [-28 - 13]
South Atlantic	16% [1 - 34]	-11% [-27 - 10]	-18% [-31 - -4]*	11% [-3 - 26]
West North Central	6% [-18 - 37]	51% [3 - 120]	4% [-27 - 46]	-6% [-35 - 36]
West South Central	31% [5 - 63]*	-24% [-45 - 3]	-9% [-28 - 15]	29% [-8 - 82]
U.S. Total	14% [9 - 20]*	24% [15 - 33]*	-2% [-9 - 4]	0% [-6 - 6]



* p<0.01

[†] Adjusted positivity rates change [95% CI] for the Pre-COVID-19 (March 13, 2019 - December 31, 2019) and the COVID-19 (March 13, 2020 - December 31, 2020) time periods. Patients with reported prescriptions for any of these medications were excluded.

States with statistically significant increases for tramadol were Tennessee, Ohio, and Kentucky. Statistically significant increases for gabapentin occurred in Virginia and Ohio. No significant changes were noted for hydrocodone or oxycodone at the state level.

Table 2. Non-Prescribed Positivity Rates for U.S. Census Divisions During the COVID-19 Time Period[†]

U.S. Census Division	Gabapentin	Tramadol	Hydrocodone	Oxycodone
East North Central	11.0% [10.1-12.0]	4.3% [3.7-4.9]	2.8% [2.4-3.3]	3.3% [2.9-3.8]
East South Central	11.3% [10.1-12.5]	3.1% [2.5-3.8]	6.3% [5.4-7.4]	4.3% [3.6-5.1]
Mid Atlantic	10.7% [9.1-12.7]	2.0% [1.5-2.6]	2.6% [2.1-3.3]	3.5% [2.8-4.3]
Mountain	8.7% [7.8-9.7]	1.8% [1.5-2.2]	2.9% [2.5-3.4]	4.3% [3.7-5.0]
New England	9.2% [6.9-12.3]	2.5% [1.6-3.7]	1.2% [0.7-2.0]	2.7% [1.8-4.1]
Pacific	8.0% [6.9-9.2]	1.7% [1.3-2.1]	3.8% [3.2-4.4]	2.6% [2.2-3.1]
South Atlantic	11.9% [10.6-13.3]	2.5% [2.1-3.0]	3.8% [3.2-4.4]	6.6% [5.8-7.6]
West North Central	9.2% [7.7-10.9]	3.0% [2.3-3.9]	3.6% [2.8-4.5]	2.6% [2.0-3.3]
West South Central	9.5% [8.1-11.1]	2.7% [2.1-3.5]	6.0% [4.9-7.3]	2.3% [1.8-2.9]
U.S. Total	9.9% [9.3-10.4]	2.5% [2.3-2.8]	3.3% [3.0-3.6]	3.4% [3.1-3.7]

[†] Adjusted positivity rates [95% CI] for the COVID-19 time period (March 13, 2020 - December 31, 2020). Patients with reported prescriptions for any of these medications were excluded.

Conclusions

These findings, combined with increasing law enforcement confiscations, suggest that tramadol remains a drug that should be monitored closely for potential misuse or diversion. There are reported cases of patients with SUD whose drug of preference is tramadol.²⁸ It will be important to continue monitoring non-prescribed tramadol use moving forward as its misuse remains a concern.

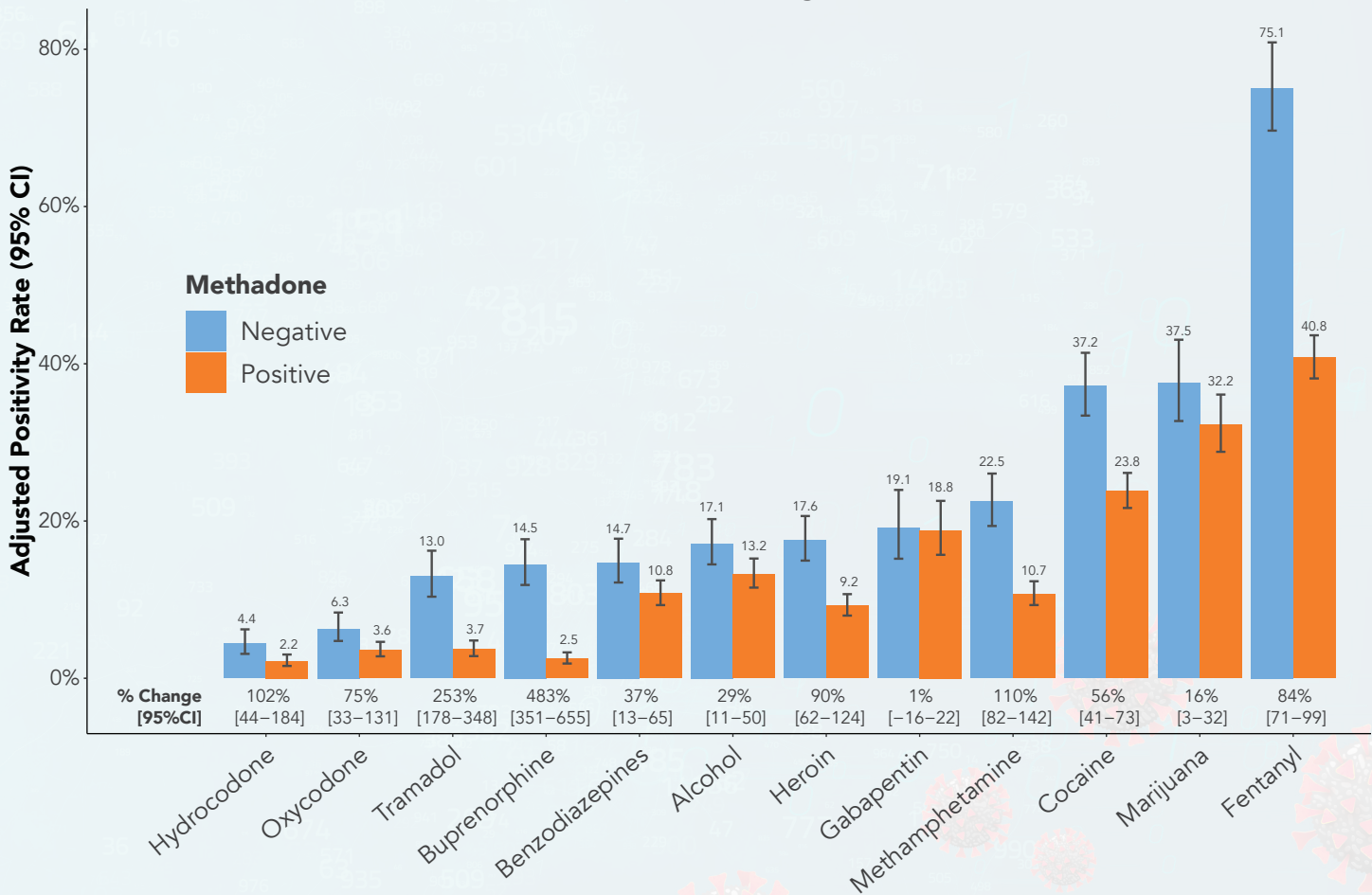
Despite some fluctuation, positivity rates of non-prescribed gabapentin have not changed substantially since being analyzed in the first

Millennium Health Signals Report and remain at approximately 10%. Lastly, despite less stringent, COVID-19-related prescribing regulations, non-prescribed hydrocodone and oxycodone positivity rates have not changed significantly, which is potentially optimistic news amidst the ongoing epidemic within a pandemic. ●

Section 4

Methadone Maintenance: Unexpected Findings Raise Risks

Figure 1. 2020 Adjusted Positivity Rates and Percent Change for 12 Non-Prescribed and/or Illicit Substances in the Population Prescribed Methadone - Stratified by Methadone Detection



The 2020 positivity rates are adjusted for age and sex in the Poisson regression models. The percent change represents the percent change in the positivity rates for the methadone-negative group and methadone-positive group.

Background

Methadone is commonly used for the treatment of opioid use disorder (OUD).²⁹ Decades of research have shown therapy with methadone keeps patients in treatment longer with lower rates of concomitant opioid use when compared to those with no medication treatment. It also helps patients stay engaged in other modalities to support their recovery.³⁰

Because of challenges in obtaining medications during the pandemic, state and federal agencies

have eased restrictions on take-home methadone doses for stable patients.¹⁴ The risk of using other substances may be amplified during the pandemic due to ongoing isolation, anxiety due to health concerns, loss of family or friends, socioeconomic factors, and other stressors.³¹ Drug testing remains an important tool in supporting recovery and monitoring for use of prescription medications, non-prescribed medications, and illicit substances.³²

Key Findings

In this section, we highlight unexpected findings for patients prescribed methadone in addiction treatment centers during 2020. Results were stratified by patients positive (consistent with treatment) or negative (inconsistent with treatment) for their prescribed methadone. Findings include:



Patients not taking prescribed methadone at the time of UDT had **significantly higher positivity rates** for **10 of the 12 non-prescribed and illicit substances** evaluated, with the exception of gabapentin and marijuana (Figure 1)



Buprenorphine, tramadol, cocaine, and fentanyl had the **largest difference** in adjusted positivity rate between the two groups (Figure 1)



Nearly **90%** of those not taking prescribed methadone and over **50%** of those positive for methadone were **also positive for 2 or more non-prescribed or illicit substances**



The most common combinations in this population prescribed methadone were **fentanyl plus another substance**, which accounted for **7 of the top 10** most common findings. Non-prescribed fentanyl alone was the **most common substance** identified (Table 1)

Methadone Maintenance: Unexpected Findings Raise Risks *(continued)*

Table 1. Top 10 Most Frequently Detected Individual or Combinations of Substances in the Population Prescribed Methadone

Ranking	1	2	3	4	5	6	7	8	9	10
Fentanyl	●	●	●	●		●	●	●		●
Methamphetamine		●					●	●		
Marijuana			●		●	●	●			
Cocaine				●		●		●		
Gabapentin									●	●

The findings are ranked 1 through 10 with number 1 (i.e. fentanyl alone) being the most common finding.

Conclusions

Patients who tested negative for their prescribed methadone had significantly higher positivity rates for almost all of the 12 non-prescribed and illicit substances evaluated than those positive for methadone. However, the majority of the methadone-positive population also had other

substances present. Identifying unexpected UDT findings in patients receiving methadone maintenance therapy suggest a possible need to adjust the treatment plan to support recovery efforts, as well as potentially mitigate risks of overdose. ●

This cross-sectional analysis includes evaluation of definitive UDT results tested by LC-MS/MS from 3.5 million unique patient specimens across the U.S. and multiple health care specialties. Specimens were collected between January 1, 2013, and December 31, 2020. Specimens with reported prescriptions were excluded from analysis, with the exception of methadone in Section 4. Poisson regression was used to adjust positivity rates by correcting for differences in population characteristics including U.S. census division, age, gender, and health care specialty.

U.S. census divisions are divided as follows: East North Central (Illinois, Indiana, Michigan, Ohio, and Wisconsin), East South Central (Alabama, Kentucky, Mississippi, and Tennessee), Mid Atlantic (New Jersey, New York, and Pennsylvania), Mountain (Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, and Wyoming), New England (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont), Pacific (Alaska, California, Hawaii, Oregon, and Washington), South Atlantic (Delaware, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, District of Columbia, and West Virginia), West North Central (Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, and South Dakota), and West South Central (Arkansas, Louisiana, Oklahoma, and Texas).

Sections 1 and 3 shows adjusted positivity rates calculated for each week between 2013 and 2020. Poisson regression was also used to test for year-over-year positivity rate changes in the Pre-COVID-19 (March 13, 2019-December 31, 2019) and COVID-19 (March 13, 2020-December 31, 2020)

time periods. March 13th was used as the starting date due to the declaration of COVID-19 as a national emergency on this date.

Section 2 analyzed positivity rates for fentanyl and fentanyl analogues from July 15, 2019, through December 31, 2020. We report findings for fentanyl, carfentanyl, and acyl fentanyl. Weekly positivity rates with binomial 95% CI values were estimated for each drug. Fentanyl analogue testing is based on a reflex strategy where testing occurs for fentanyl analogues following a positive test result for fentanyl or norfentanyl. For additional methodology information on fentanyl analogue testing, see Stanton et al.⁷

Section 4 analyzed specimens collected in 2020 from patients in substance use disorder treatment facilities who were prescribed methadone. Poisson regression was then used to evaluate the impact of methadone status (positive or negative) on 12 non-prescribed or illicit drugs. Positivity rates for the 12 drugs were adjusted for age and sex in the model. Marginal positivity rates (Least Square Means) and Relative Risk (incidence rate ratio) values converted to percent change were estimated for all models. Percent change and 95% CI values for positivity rates were Sidak-corrected and p-values were Tukey-corrected to control for multiple comparisons.

R statistical software version 3.5.0 (R Project for Statistical Computing) was used for data analysis. Statistical significance was set at P less than 0.01, and all tests were 2-tailed. ●

Conclusion



Michael S. Parr, MD, FASAM

Board Certified in Addiction Medicine, Certified Interventionist

The year 2020 marked a humanitarian crisis in the United States in more ways than one. Americans' mental health has suffered due to impacts of the pandemic, including isolation, loss of jobs, homes, and economic stability, anxiety of contracting illness, deaths of family and friends, and a sense of desperation emerging for some. This has led many, and I've seen this firsthand in my practice, to reach for any available drug to alter their reality. Even more concerning, addiction treatment remains inaccessible for most.

The first three sections of this report compare drug use trends in the years before the pandemic to the 9 months after the declaration of a national emergency on March 13, 2020, a year that won't soon be forgotten. The data emphasizes that when observing drug use trends, a complicated picture emerges. Drug use has likely been affected in numerous ways by the pandemic and continues to shift, often exhibiting regional variations that must be considered. Additionally, it's clear that labeling the drug use epidemic in this country an "opioid crisis" has now become a misnomer.

A recent study by Wang et al.² concluded that individuals with SUD, particularly OUD, are an especially vulnerable population when it comes to increased risk of adverse outcomes from COVID-19, and that it is important to screen and treat SUD as part of the complete picture of controlling pandemic-related effects. The first section of this report identified increases in non-prescribed

fentanyl across every division of the country, indicating that illicitly manufactured fentanyl will likely continue to drive drug overdose deaths for the foreseeable future. Patients must be made aware of the risks of fentanyl, as well as the potential for fentanyl to be an unknown contaminant even if their drug of preference is not an opioid. It may also be prudent to consider pre-emptively prescribing naloxone for patients with past or current history of SUD, especially OUD. Additionally, the rising use of methamphetamine has several implications that pose unique challenges. It's important to remember that when using UDT as a monitoring tool to improve the therapeutic alliance with patients in treatment that clinicians are aware of differences in immunoassay versus definitive tests for methamphetamine.

There are a few silver linings in this report. The major decrease in positivity for carfentanil is good news for patients and the clinicians caring for them. This is especially true of carfentanil, which at 100 times the potency of fentanyl, is one of the most potent drugs available today.

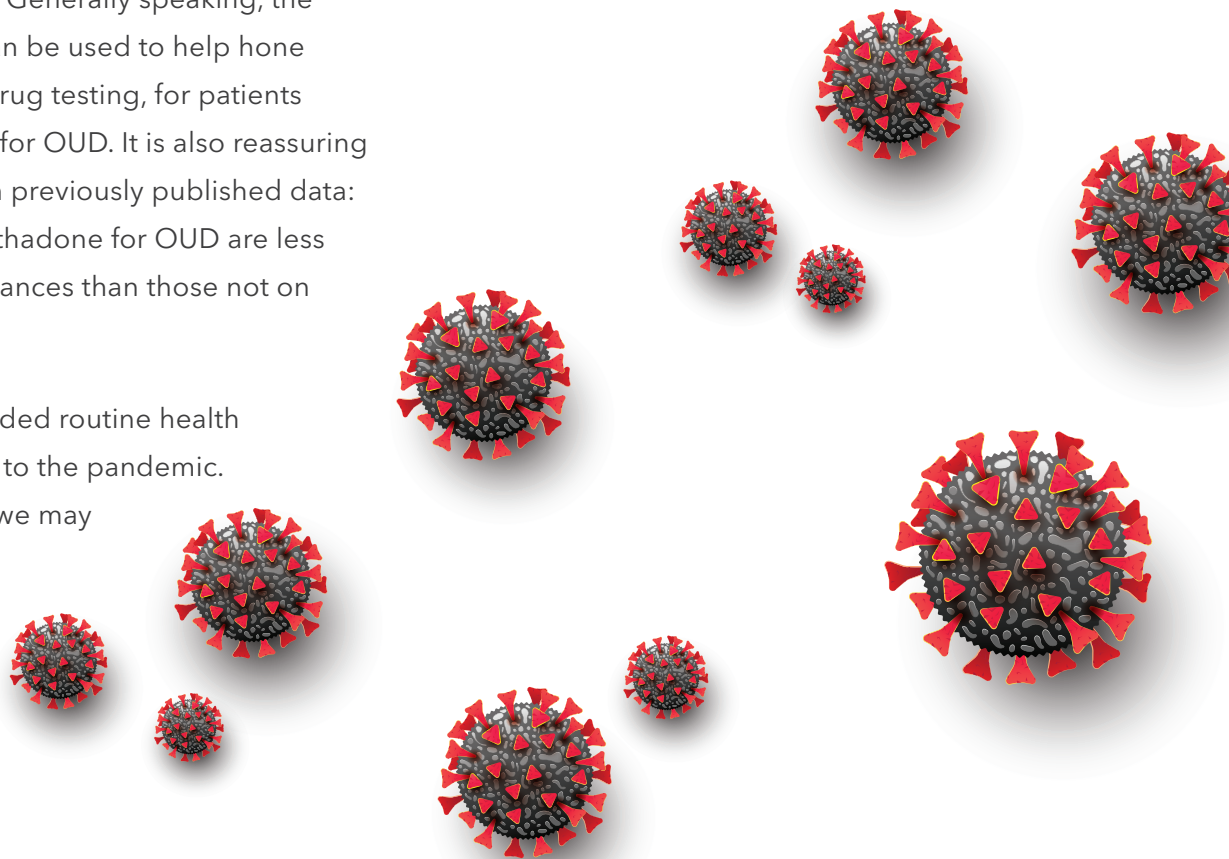
Despite the hardships faced during the pandemic, it is encouraging to see that positivity rates for non-prescribed use of hydrocodone and oxycodone have not changed. Patients requiring opioids for the treatment of pain have faced difficulty obtaining medications, as well as stigma, before the pandemic. Perhaps this data will reassure clinicians who have taken additional steps to safely prescribe these

medications during the pandemic. It's also important to remember that tramadol is an opioid agonist, and treat it as such. Though there was an increase in positivity of non-prescribed tramadol, this was specifically in Ohio, Tennessee, and Kentucky, again revealing a potential for targeted measures in certain geographical areas. This trend will also bear watching in the future.

Finally, this report evaluated unexpected findings for methadone with other non-prescribed and illicit substances throughout 2020. We see the resonance of fentanyl looming at every turn, as this again is the number one drug found in the population prescribed methadone. Generally speaking, the results of this section can be used to help hone monitoring, including drug testing, for patients prescribed methadone for OUD. It is also reassuring to see concurrence with previously published data: patients prescribed methadone for OUD are less likely to use other substances than those not on medication therapy.

Some people have avoided routine health screenings in 2020 due to the pandemic. Therefore, it's possible we may see an emergence of even more patients needing treatment for SUD once the pandemic is over, which underscores the importance

of expanding access to SUD treatment to meet the current and emerging need. Ongoing information about which drugs are being used in a real-time fashion helps clinicians monitor and treat patients, as well as direct efforts by those in the public health sphere, including education, prevention, and harm reduction. Additionally, research is currently underway for novel modalities for the treatment of SUD, including new medications. The CDC and others continue to encourage the use of non-traditional data sources, such as laboratory data, to rapidly identify changes in the drug use landscape.^{3,33} ●



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A Thank You to Our Expert

Michael S. Parr, MD, FASAM*

Board Certified in Addiction Medicine, Certified Interventionist

Contributors

Brandon Adkins, PharmD

Toxicologist

William Bundy, PharmD

Toxicologist

Louis Canales

Director of Data Services

Maria Chianta, PharmD

National Director, Managed Markets Medical Liaison

Jenna Curammeng

Associate Manager, Creative

Eric Dawson, PharmD

Vice President, Clinical Affairs

Monica Fileger, D-ABFT

Toxicologist

Joy Griffin, RN, BSN

Associate Director, Clinical Resource Specialist

Maria G. Guevara, PharmD, CPE

Director of Clinical Affairs, Education & Training

Leah LaRue, PharmD, PMP

Director, Scientific Communications

Kelly Olson, PhD

Associate Director, Clinical Affairs

Adrian Rios

Sr. BI Architect

Adam Rosendorff, MD

Medical Director

Ian Smith

Sr. Tableau Developer

Joseph Stanton, PhD

Associate Director, Clinical Affairs

Javier Velasco, PhD

Toxicologist

Penn Whitley

Director of Bioinformatics

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