

# Fentanyl: A substance of great concern

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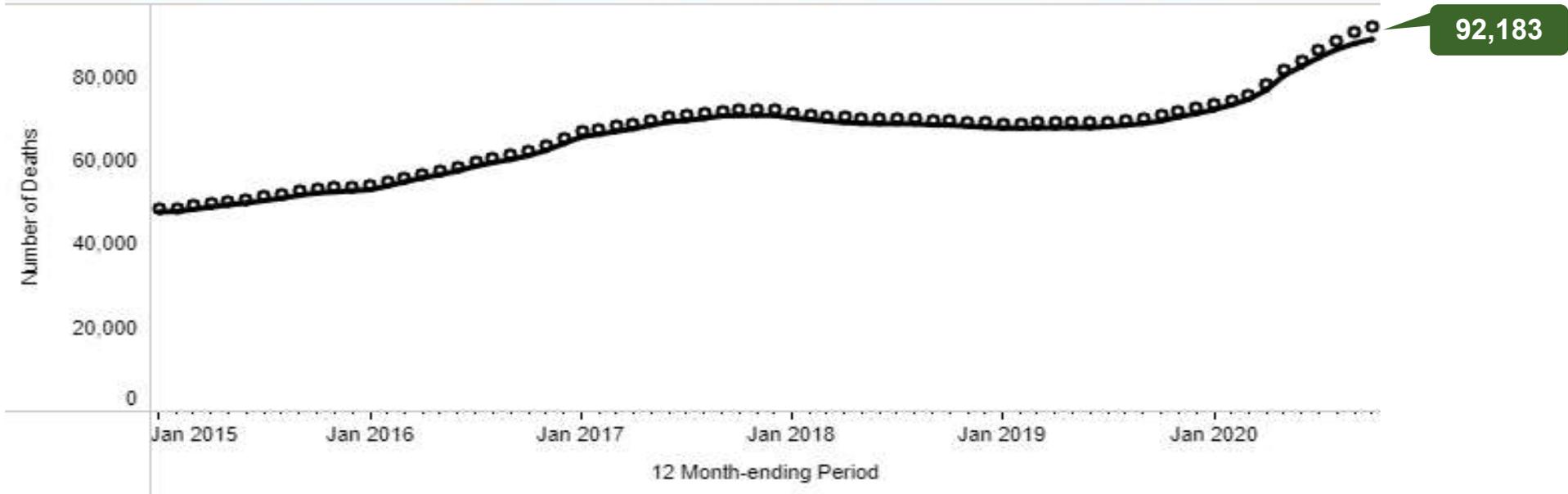
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# The drug misuse epidemic in the US

Drug overdose deaths at an all-time high (Up 29.4% in 2020 over 2019)

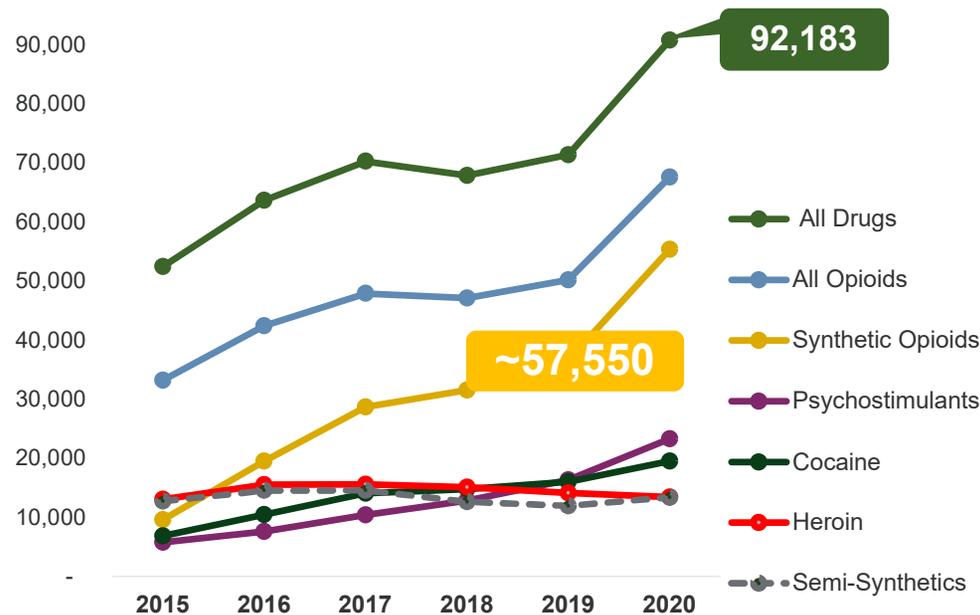
12-month–ending period provisional counts of drug overdose deaths: United States<sup>1</sup>



1. CDC, National Vital Statistics System Rapid Release. Accessed June 7, 2021. [www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm](http://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm)

# The drug misuse epidemic in the US

## Fentanyl is driving the most overdoses<sup>1</sup>



- An estimated 57,550 people died of overdoses from synthetic opioids, primarily fentanyl, an increase of more than 54% over 2019

1. CDC, *National Vital Statistics System Rapid Release*. Accessed June 7, 2021. [www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm](http://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm)

# The opioid epidemic within the COVID-19 pandemic: drug testing in 2020

## Study methods

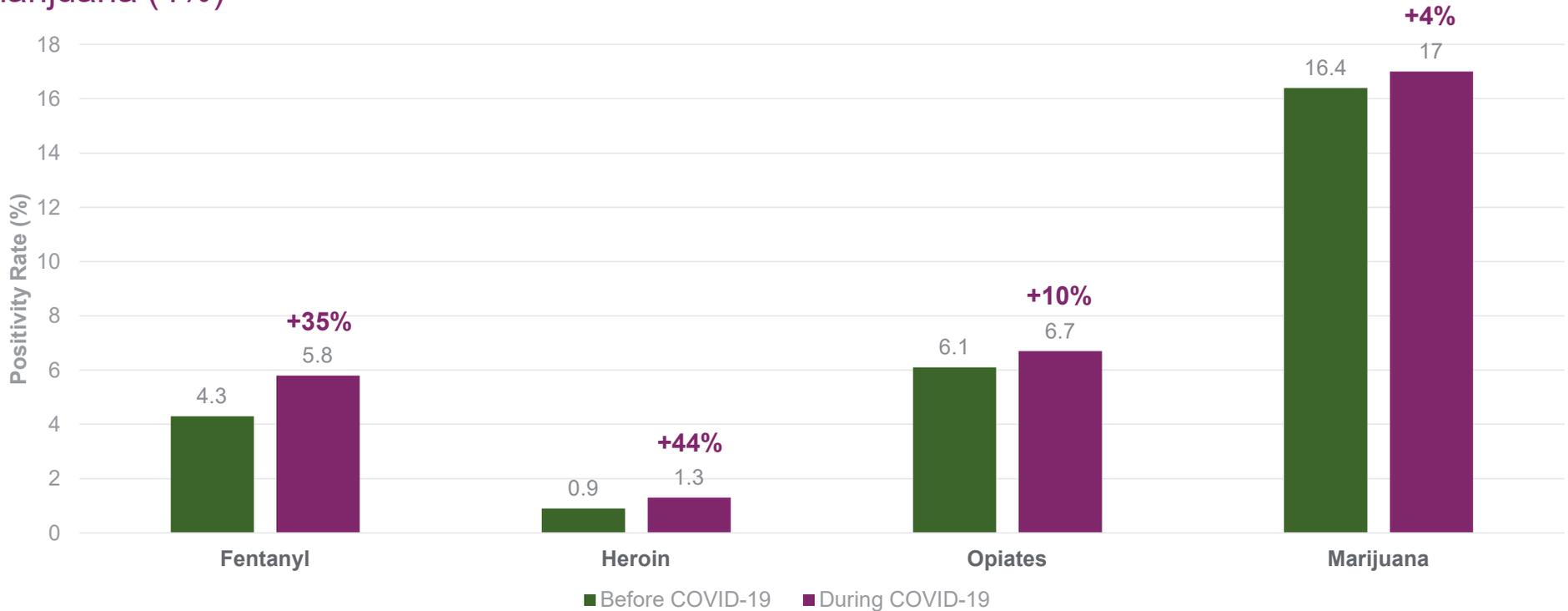
- This study analyzed urine specimen results from the Quest Diagnostics medMATCH® reporting methodology for clinical drug testing
  - medMATCH® reports indicate whether prescribed drug(s) specified by ordering provider, or other drugs, are detected in a specimen
- Deidentified urine drug testing (UDT) results from January 1, 2019, to May 16, 2020, were obtained from the Quest Diagnostics database
  - Results were included if prescription drug information was available for patients >18 years
- Weekly testing volume and drug positivity rates for nonprescribed fentanyl and illicit drugs were compared between a baseline period (January 1, 2019-March 14, 2020) and a COVID-19 pandemic period (March 15-May 16, 2020)
  - The week starting March 15 was the first full week after a national emergency was declared on March 13
- Positivity for nonprescribed drugs was defined as the presence of a positive result for any drugs not listed as prescribed by the ordering clinician, or for recreational/illicit drugs
- Analysis of results included either presumptive immunoassay screening tests, with confirmation of positive results by quantitative definitive mass spectrometry, or tests performed directly by quantitative definitive mass spectrometry

A total of 881,134 specimens were identified that met the criteria for potential inclusion in the study

- Specimens were excluded for patients younger than 18 years of age and those without known age (n = 8139)
- Specimens with abnormal specimen validity testing and no positive drug results (n = 233) also were excluded, leaving a final analytic cohort with 872,762 specimens (99% of potential cohort) from all 50 states and the District of Columbia

# Positivity for nonprescribed fentanyl increased by 35%<sup>a</sup> (4.3% to 5.8%, $P < .01$ ) during COVID-19 pandemic

Significant increases in positivity also demonstrated for heroin (44%), opiates (10%), and marijuana (4%)<sup>b</sup>



a. Significance analyzed with Chi-square test.

b.  $P < .01$  for all listed substances.

Source: Quest Diagnostics Health Trends™. January 2020– December 2020.

# About Fentanyl

# History of Rx fentanyl

Fentanyl: a short-acting synthetic opioid – not derived from the poppy plant

1959

Fentanyl first synthesized by Paul Janssen in order to advance the understanding of opioid receptors<sup>1</sup>  
Derived from the synthetic opioid meperidine

1968

Fentanyl citrate enters medical use<sup>2</sup>  
An aqueous solution for IV or IM injection under Trade name Sublimaze  
Used as a surgical anesthetic

1990

Duragesic<sup>®</sup> patch introduced to broaden utility beyond Surgical Anesthesia  
It circumvented the short duration of action of fentanyl by allowing drug to be absorbed over 48-72 hour period<sup>3</sup>  
Discontinued, 2020<sup>4</sup>

1998

Short/Rapid acting fentanyl finds place for treatment of breakthrough cancer pain  
Actiq<sup>®</sup> approved but with additional safety measures including approval for **REMs** in 2011 for **transmucosal immediate release fentanyl (TIRF)** products<sup>5</sup>

1. Schulz W. Fentanyl. Chemical and Engineering News. American Chemical Society. 2005. <https://pubs.acs.org/cen/coverstory/83/8325/8325fentanyl.html>
2. McNeil Laboratories. Fentanyl (Sublimaze). Clin Pharmacol Ther. 1968;9(5):704-706. doi:10.1002/cpt196895704
3. Duragesic (fentanyl transdermal system) [prescribing information]. Janssen; August 2021.
4. US Food and Drug Administration (FDA). FDA Drug Shortages. Current and Resolved Drug Shortages and Discontinuations Reported to FDA. Fentanyl (Duragesic 100, 12, 25, 37, 50, 75) Extended-Release Film. April 1, 2020. Accessed at: <https://www.accessdata.fda.gov/DURAGESIC>
5. FDA. Timeline of selected FDA activities and significant events addressing opioid misuse and abuse. <https://www.fda.gov/drugs/information-drug-class/timeline-selected-fda-activities-and-significant-events-addressing-opioid-misuse-and-abuse>.

## Illicitly derived fentanyl

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### Origins of the opioid epidemic provided foundation for the synthetic opioid epidemic

- **1998-2008**
  - Opioid overdose deaths tripled prompting the CDC to declare that the US was in the midst of an **opioid epidemic**
  - Due to National attention and widespread efforts opioid prescriptions have declined
    - According to an IQVIA report, prescription opioid use declined by 60% from 2011 peak to expected 2020 levels.<sup>6</sup>
- However, as opioid prescribing declined people with opioid use disorder began to turn to the illicit drug market for **Heroin**
- This paved the way for the illicit drug market to find its **footing in fentanyl production**

6. Prescription opioid use in the U.S. has declined by 60% from 2011 peak, according to new report from the IQVIA™ Institute for Human Data Science. IQVIA press release. December 17, 2020.

## Illicit fentanyl production: displacing fentanyl

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### The poppy plant is not required in order to make fentanyl!

- Many natural (ie, heroin) or semi-synthetic opioids (i.e., hydrocodone, oxycodone) come from the resin of the Opium Poppy (*Papaver Somniferum*)
- The process of growing the poppy plant, harvesting the resin, and processing it into the final product is what makes heroin expensive and creates a profit margin less desirable for illicit drug producers
- Fentanyl is purely synthetic and can be made by a single person in a lab
  - More profitable and easier to produce than heroin
  - A 2019 DEA report estimated that each fentanyl pill costs only \$1 to produce. It can be resold in the US for at least 10 times as much<sup>7,8</sup>

7. Travère A, Giraudat J. Revealed: how Mexico's Sinaloa cartel has created a global network to rule the fentanyl trade. The Guardian. December 8, 2020. <https://www.theguardian.com/world/2020/dec/08/mexico-cartel-project-synthetic-opioid-fentanyl-drugs>

8. <https://www.npr.org/2020/11/17/916890880/we-are-shipping-to-the-u-s-china-s-fentanyl-sellers-find-new-routes-to-drug-user>

## Where is the fentanyl coming from?<sup>7,8</sup>

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- **Powdered fentanyl** is synthesized and processed in Southeast Asia or Mexico, mixed with heroin and sold as heroin in the US
  - May also be pressed into pills looking like a Rx opioid
  - Powdered fentanyls are cut and diluted at any time with other drugs for further smuggling
- **Precursors** for manufacturing fentanyl are shipped to the US and cartels in Mexico
  - Precursors are used to manufacture fentanyl in clandestine labs

### Precursors

- 4-aniline-N-phenethylpiperidine (4-ANPP)
- N-phenethylpiperidine (NPP)

7. Travère A, Giraudat J. Revealed: how Mexico's Sinaloa cartel has created a global network to rule the fentanyl trade. The Guardian. December 8, 2020. <https://www.theguardian.com/world/2020/dec/08/mexico-cartel-project-synthetic-opioid-fentanyl-drugs>

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## Where is the fentanyl coming from?<sup>7,8</sup>

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Historically Southeast Asia produced most of the illicit fentanyl. This is changing....

- Until recently, most of the fentanyl came out of China and Southeast Asia. Stricter international regulations and a **Chinese Crackdown in 2019** made the shipping of illicit fentanyl riskier
- However, china remains the main producer of the precursor chemicals used for the synthesis of fentanyl
  - Often sold as “research chemicals”
  - Makeshift pharmaceutical companies have even sold fentanyl precursors on social media platforms
- In addition, ‘new synthetic opioids’ (NSO) often derived from fentanyl are emerging. Also known as fentanyl analogs
  - Varying potencies
  - Often found as cutting agents in fentanyl and/or heroin products
  - Also sold as ‘research chemicals’ online

7. Travère A, Giraudat J. Revealed: how Mexico's Sinaloa cartel has created a global network to rule the fentanyl trade. The Guardian. December 8, 2020. <https://www.theguardian.com/world/2020/dec/08/mexico-cartel-project-synthetic-opioid-fentanyl-drugs>

8. <https://www.npr.org/2020/11/17/916890880/we-are-shipping-to-the-u-s-china-s-fentanyl-sellers-find-new-routes-to-drug-user>

# Fentanyl analogs

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- Fentanyl analogs, which are similar in chemical structure to fentanyl but not routinely detected because specialized toxicology testing is required
- Recent surveillance has also identified other emerging synthetic opioids, like **U-47700**<sup>5</sup>
- Estimates of the potency of fentanyl analogs vary from **less potent than fentanyl to much more potent than fentanyl**, but there is some uncertainty because potency of illicitly manufactured fentanyl analogs has **not been evaluated in humans**
- Carfentanil, the most potent fentanyl analog detected in the US, is estimated to be 10,000 times more potent than morphine<sup>9,10</sup>

- **Acetylfentanyl**
- **Acrylfentanyl**
- **Butyrfentanyl**
- **Carfentanil**
- **Furanylfentanyl,**
- **Despropionylfentanyl**

9. O'Donnell JK, Halpin J, Mattson CL, Goldberger BA, Gladden RM. Deaths Involving Fentanyl, Fentanyl Analogs, and U-47700 — 10 States, July–December 2016. MMWR Morb Mortal Wkly Rep 2017;66:1197–1202.

10. O'Donnell J, Gladden RM, Mattson CL, Kariisa M. Notes from the Field: Overdose Deaths with Carfentanil and Other Fentanyl Analogs Detected – 10 States, July 2016–June 2017. MMWR Morb Mortal Wkly Rep. July 2018. 67(27);767–768.

# Drug Monitoring

## Why should you drug test?

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- Manage prescription drug use
  - Positive for prescribed drug(s) of interest
  - Negative for illicit drugs and other prescribed drugs
- Objectively analyze adherence to the plan
- Help diagnose substance misuse, abuse, and addiction
- Identify patients who may be diverting medications
- Meet expectations of medical boards and regulatory agencies
- Advocate for patients
- Help PROTECT YOURSELF

### Fentanyl Potency!

- 50x > Heroin
- 100x > Morphine

Source: Heit HA, Gourlay DL. *J Pain Symptom Manage.* 2004;27:260-267.

# Medical and public health organizations support drug testing

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- CDC Guidelines for Prescribing Opioids for Chronic Pain (March 2016)<sup>11</sup>
  - *“When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs.”*
- The American Association for Clinical Chemistry (AACC) Academy–Laboratory Medicine Practice Guidelines: Using Clinical Laboratory Tests to Monitor Drug Therapy in Pain Management Patients (November 2017)<sup>12</sup>
  - *“Based on level II evidence, baseline drug testing should be performed prior to initiation of acute or chronic controlled substance therapy. In addition, random drug testing should be performed at a minimum of one to two times a year for low-risk patients (based on history of past substance abuse/addiction, aberrant behaviors, and opioid risk screening criteria), with increasing frequency for higher-risk patients prescribed controlled substances.”*
- The American Society of Addiction Medicine (ASAM) Appropriate Use of Drug Testing in Clinical Addiction Medicine, consensus statement (April 2017)<sup>13</sup>
  - *“Drug testing should be a routine part of initial and ongoing patient assessment of recent substance use in all addiction treatment settings.”*

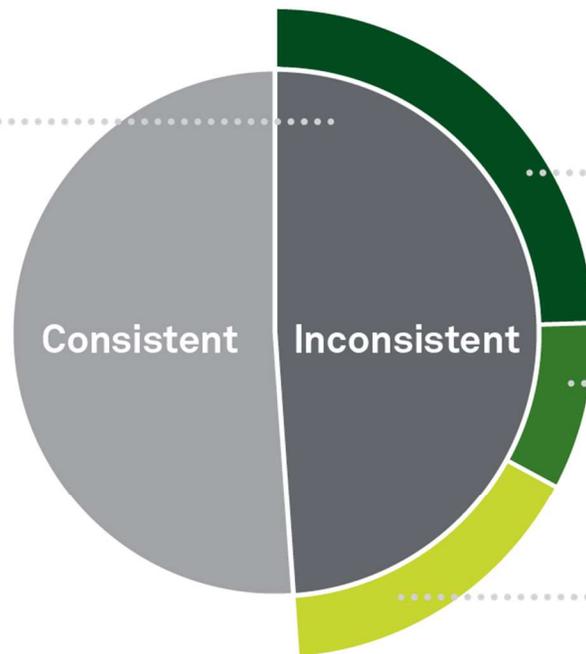
11. CDC Guidelines for Prescribing Opioids for Chronic Pain. <https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm>

12. AACC. <https://www.aacc.org/science-and-practice/practice-guidelines/using-clinical-laboratory-tests-to-monitor-drug-therapy-in-pain-management-patients>

13. ASAM. [https://journals.lww.com/journaladdictionmedicine/Fulltext/2017/06000/Appropriate\\_Use\\_of\\_Drug\\_Testing\\_in\\_Clinical.1.aspx](https://journals.lww.com/journaladdictionmedicine/Fulltext/2017/06000/Appropriate_Use_of_Drug_Testing_in_Clinical.1.aspx)

# Quest drug testing data shows that nearly half of patients misuse their medications

**48%**  
of Quest's drug monitoring tests showed signs of misuse



## Additional drugs are found

**49%** combined prescribed drug(s) with at least one other nonprescribed or illicit drug

## Different drugs are found

**18%** did not show prescribed drugs, but were positive for at least one other nonprescribed or illicit drug

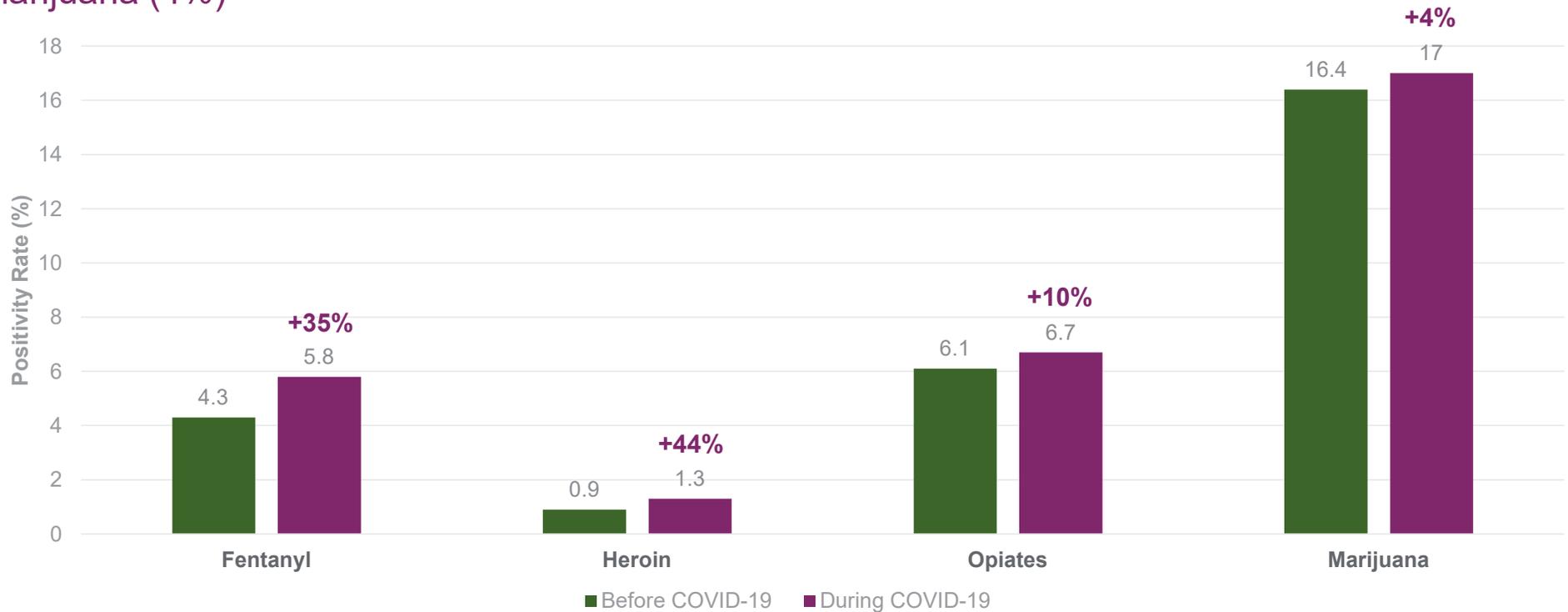
## No drugs are found

**33%** did not show the prescribed drugs or any other tested drug

Source: Quest Diagnostics Health Trends™. January 2020– December 2020.

# Positivity for nonprescribed fentanyl increased by 35%<sup>a</sup> (4.3% to 5.8%, $P < .01$ ) during COVID

Significant increases in positivity also demonstrated for heroin (44%), opiates (10%), and marijuana (4%)<sup>b</sup>



a. Significance analyzed with Chi-square test.

b.  $P < .01$  for all listed substances.

Source: Quest Diagnostics Health Trends™. January 2020– December 2020.

# Presumptive versus definitive testing

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## What are we missing?

- Based on historical/known data on accuracy of presumptive testing (for example, by POCT cup or dipstick), we hypothesized that presumptive-only testing would miss an unacceptable amount of true positive results for fentanyl when compared to definitive testing, due to the higher cutoffs of presumptive testing
- Of the 20,068 samples tested for fentanyl, **14,808 (74%)** of the results were between the definitive cutoff value of **0.5** and presumptive cutoff value of **200 ng/ml**

# Protracted renal clearance of Fentanyl in persons with OUD

**Fentanyl** detected up to **19 days** and **Norfentanyl** up to **26 days!**

## Protracted renal clearance of fentanyl in persons with opioid use disorder

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### ARTICLE INFO

#### Keywords:

Fentanyl  
Opioid use disorder  
Pharmacokinetic  
Heroin  
Opioid  
Treatment

### ABSTRACT

**Introduction:** The illicit opioid supply in the U.S. is increasingly adulterated with fentanyl. As such, persons with opioid use disorder (OUD) may be regularly exposed to fentanyl, however, the pharmacokinetics of repeated fentanyl exposure are not well understood. The current study aimed to quantify renal clearance of fentanyl in OUD patients presenting to residential treatment.

**Methods:** Participants (N = 12) who presented to a 28-day residential treatment program were enrolled if they tested positive for fentanyl at intake. Urine samples were collected every 2–3 days and were quantitatively tested for fentanyl, norfentanyl, and creatinine via liquid chromatography mass spectrometry (LC–MS). Fentanyl clearance was defined as the time since last illicit opioid use and the median time between last positive and first negative fentanyl urine screen.

**Results:** Participants had a mean and standard deviation (SD) age of 28.9 (11.0), were 67 % male, and 83 % white. The mean (SD) time for fentanyl and norfentanyl clearance was 7.3 (4.9) and 13.3 (6.9) days, respectively. One participant continued to test positive for fentanyl for 19 days and norfentanyl for 26 days following their last use, and left treatment without testing negative for norfentanyl.

**Conclusion:** Fentanyl clearance in persons with OUD is considerably longer than the typical 2–4 day clearance of other short-acting opioids. The findings of this study might explain recent reports of difficulty in buprenorphine inductions for persons who use fentanyl, and point to a need to better understand the pharmacokinetics of fentanyl in the context of opioid withdrawal in persons who regularly use fentanyl.

## Can incidental exposure cause a positive drug test for Fentanyl?

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- It might. We detect the fentanyl metabolite (Norfentanyl) as low as 0.5 ng/mL

Drug/Drug Class	Presumptive Cutoff (ng/mL)	Definitive Cutoff (ng/mL)	Reportable Drug or Metabolite	Additional Reportable Drug/Metabolite <sup>e</sup>
Fentanyl	0.5	0.5	Fentanyl Norfentanyl	Norfentanyl

# Considerations for implementing a responsible testing protocol

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## Key elements of a drug monitoring protocol when prescribing controlled medications<sup>1</sup>:

1. Establish which individuals to monitor
2. Evaluate patient risk factors using validated tools
3. Review the state Prescription Drug Monitoring Program (PDMP)
4. Create written treatment agreements
5. Discuss the risks and benefits of therapy
6. Review patient responsibilities
7. Conduct baseline testing
8. Conduct periodic, risk-based drug monitoring

1. Adapted from Adler JA and Jackson WC. Implementing a prescription drug monitoring protocol to ensure responsible opioid prescribing. *Pain Medicine News*. September 2018.

# Completing the protocol

## Determining which drugs to test

### How to determine which drugs to test

Drugs should be selected based on patient history, treatment plan, health condition, and community usage. Common drug class tests may include but are not limited to the following<sup>1</sup>

- Alcohol Metabolites
- Amphetamines
- Barbiturates
- Benzodiazepines
- Buprenorphine
- Cocaine
- **Fentanyl**
- Heroin
- Marijuana
- Methadone
- Opiates
- Oxycodone



1. Adapted from Adler JA and Jackson WC. Implementing a prescription drug monitoring protocol to ensure responsible opioid prescribing. *Pain Medicine News*. September 2018.

# Completing the protocol (continued)

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## Determining frequency of testing



### How to determine frequency of testing

Identify patients at high risk for opioid abuse, misuse, or diversion for whom more intensive monitoring may be appropriate<sup>1</sup>

- Validated risk assessment and stratification
- Clinician's documented medical necessity
- Patient history, clinical presentation, and/or community usage

1. Adapted from Adler JA and Jackson WC. Implementing a prescription drug monitoring protocol to ensure responsible opioid prescribing. *Pain Medicine News*. September 2018.

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