

Opioid History with Fentanyl Evolving Trends How We Got Here!

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Presentation Objectives

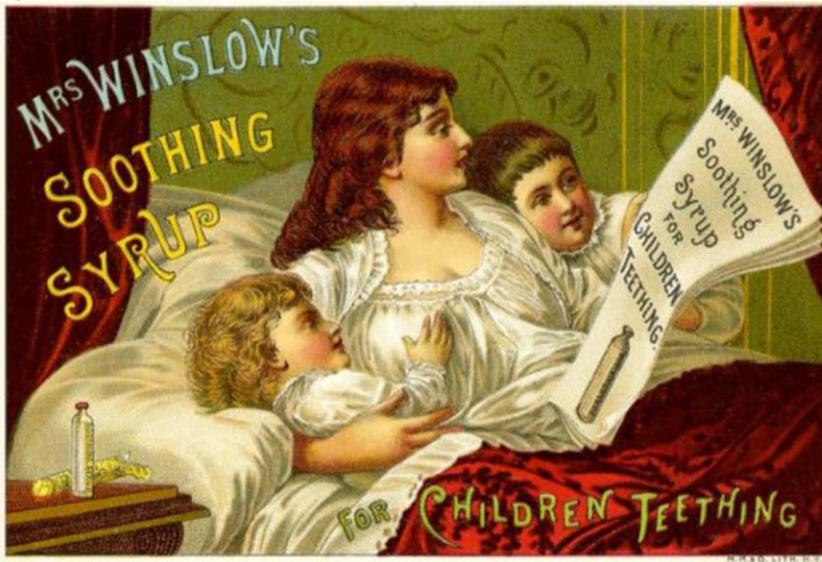
- Opioid abuse has been a world problem for centuries and predates the United States issues the last 25 years. A quick review of opium abuse in China and the United States during the 1800's.
- Review of the current fentanyl abuse and prevalence in CRL's urine and oral fluid testing population.



United States Early Involvement with Drugs

- Using drugs in the US has a substantial history with cocaine, marijuana, heroin, and opium.
- This lasted until the Harrison Narcotic Act of 1914 which created the controlled substances and restricted free commercial trade as a product or in combination as the “extra special” ingredient. The original drugs were heroin and cocaine.
- A few vintage slides to share as we learned about the dangers of them and addiction that often followed.

Vintage Ads for When Cocaine, Marijuana, and Heroin were Legal 1880-1920

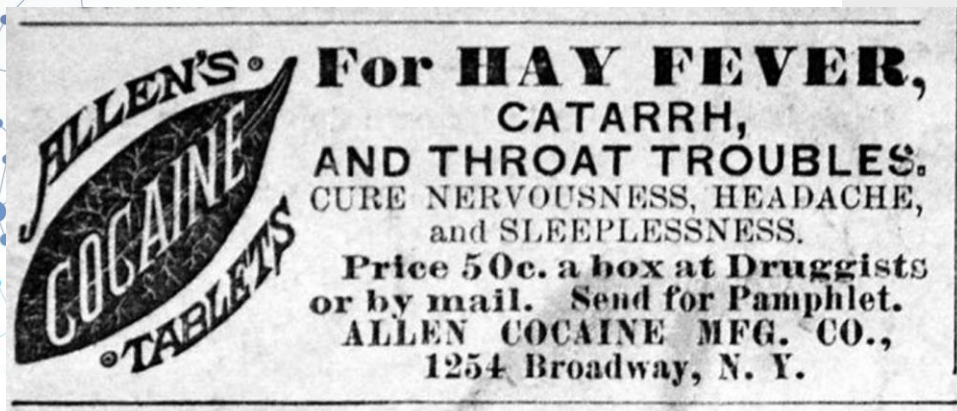


This product was first bottled in Bangor, Maine, in 1849 and contained a healthy dose of morphine. It was often used to treat teething babies.

My grandmother was a big believer in whiskey on the gums!



Products like heroin cough drops and cocaine-laced toothache medicine were sold openly and freely over the counter, using colorful advertisements



ALLEN'S
COCAINE
TABLETS

For HAY FEVER,
CATARRH,
AND THROAT TROUBLES.
CURE NERVOUSNESS, HEADACHE,
and SLEEPLESSNESS.

Price 50c. a box at Druggists
or by mail. Send for Pamphlet.
ALLEN COCAINE MFG. CO.,
1254 Broadway, N. Y.



COCA-COLA
SYRUP & AND & EXTRACT.

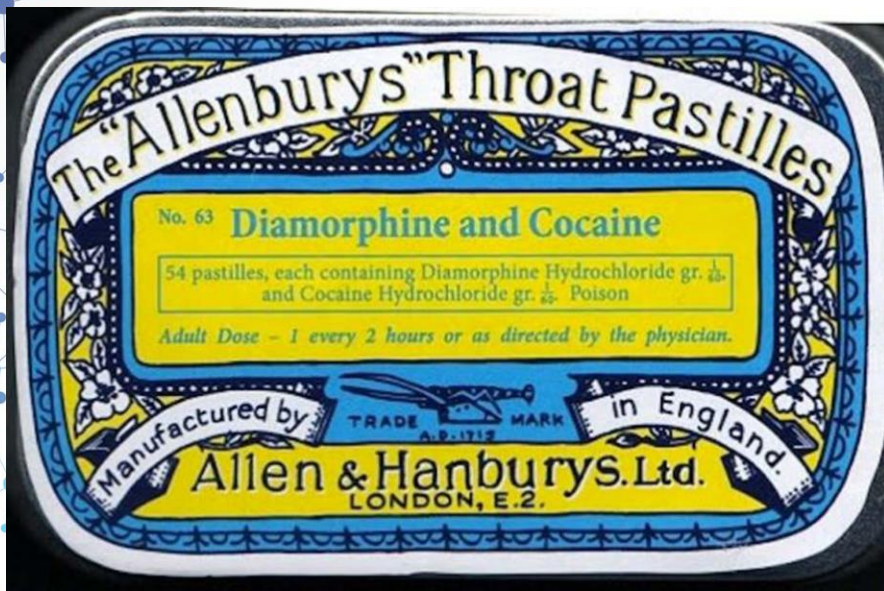
For Soda Water and other Carbonated Beverages.

This "INTELLECTUAL BEVERAGE" and TEMPERANCE DRINK contains the valuable TONIC and NERVE STIMULANT properties of the Coca plant and Cola (or Kola) nuts, and makes not only a delicious, exhilarating, refreshing and invigorating Beverage, (dispensed from the soda water fountain or in other carbonated beverages), but a valuable Brain Tonic, and a cure for all nervous affections — SICK HEAD-ACHE, NEURALGIA, HYSTERIA, MELANCHOLY, &c.

The peculiar flavor of COCA-COLA delights every palate; it is dispensed from the soda fountain in same manner as any of the fruit syrups.

J. S. Pemberton;
Chemist,
Solo Proprietor, Atlanta, Ga.



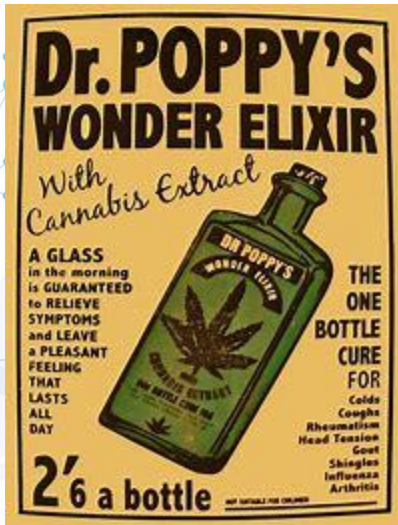
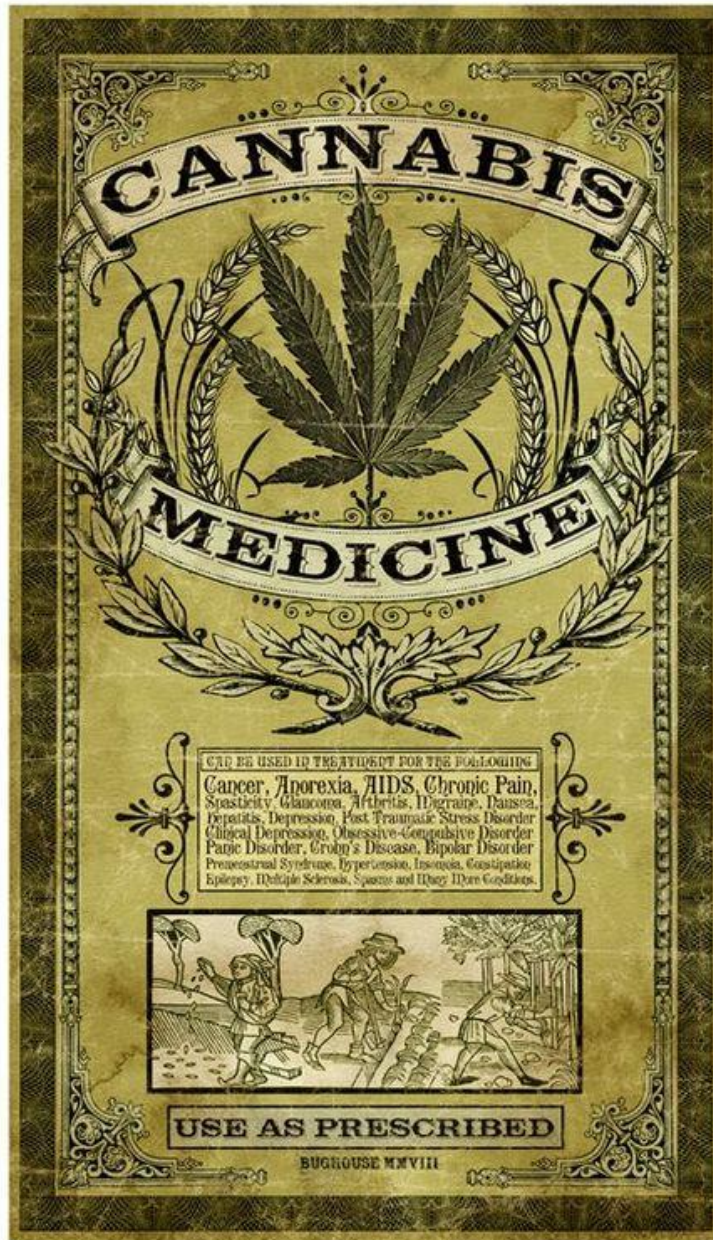


7 mg of cocaine per ounce



Confidential





Brief History on the Opium Trade Between Great Britain and China



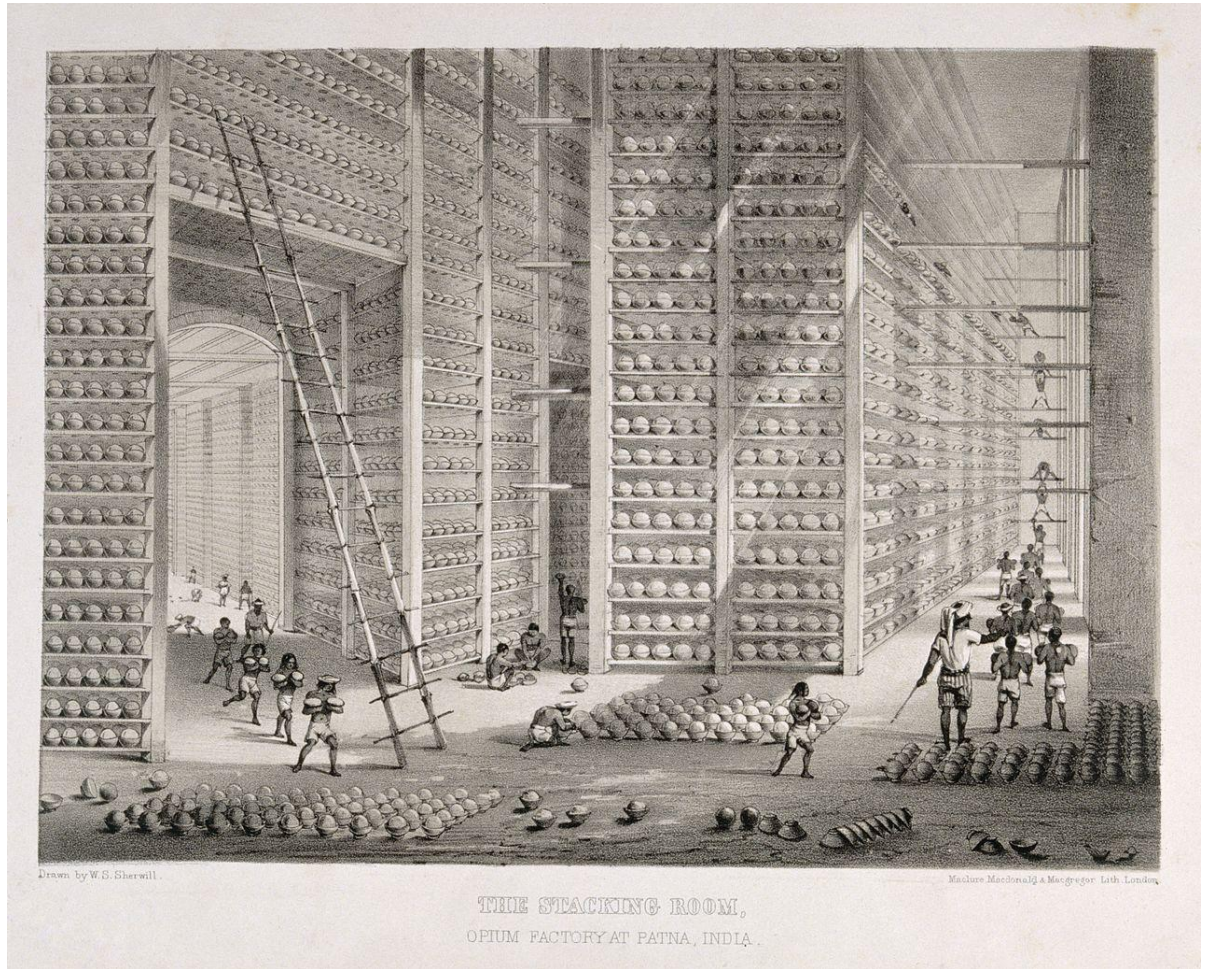
Opium Origins

- Opium, also referred to as poppy tears, is the dried latex from the seed capsule of the opium poppy *Papaver somniferum*.
- Seeds date back to 5000 BC with the oldest record going back to 2100 BC. It was not until the 1st century that the milky juice of the poppy was used prior to surgery.
- Opium was introduced into China in the 7th century for medicinal use.
- By 1000 AD the Arabic physicians were using opium medically for diarrhea and other conditions. Tinctures of opium (paregoric) are still available for GI conditions as they control intestinal spasms.
- The countries around the Mediterranean Sea had grown opium for more than a thousand years and eventually traded opium via the Silk Road. Opium was also grown in India for sale to China by the British East India Company.
- By the 1600's the British East India Company began shipping opium to China via Chinese smugglers. This led from medicinal to recreational smoking/addictions with creation of opium dens due to the abundance of opium. By the 1800's it was claimed nearly 1/3rd of the Chinese population were addicted.
- By the 18th century opium was regularly used in England as a medical treatment to replace arsenic and mercury. It also became the treatment for cholera, and dysentery ailments.

British East India Company Background and Involvement in the Opium Wars

- Private corporation that formed in 1600 to establish a British presence in the India spice trade to compete with Spain and Portugal. The British taxation on tea was a catalyst for the Boston Tea Party (December 16, 1773) and the American Revolution.
- Employed a private army of 200,000 to protect their trade and expand its territories.
- It used its army to subdue Indian states, enforce taxation, and exploited skilled and unskilled Indian Labor.
- The Indian rebellion brought about the abolishment of the East India Company in 1858.
- The East India Company was nationalized by the British government in 1858 and dissolved in 1874 after nearly three centuries.

Opium Storage
at a British East
India Company
Warehouse in
Patna, India
around 1850.
Building about
10 floor's high.



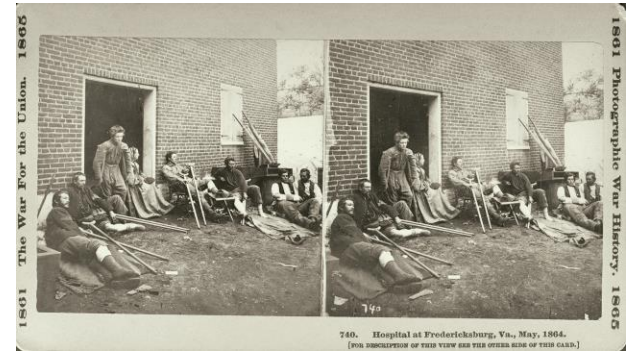
Opium Wars Between England and China

Beginnings of Illicit Opium Trade

- The Qing dynasty tried to ban opium four times from 1829-1831 but illegal imports grew rapidly. In 1839 the Chinese government destroyed 1,400 tons of opium which led to war with Britain.
- In 1839 Britain East India Company invaded China to crush opposition to trading rights with China. China had a traditional trade surplus with sale of porcelain, silk, and tea in exchange for silver. The British East India Company countered and sold opium for silver.
- The war ended in 1842 in which China ceded Hong Kong Island (*Treaty of Nanking*) to the Britain for financial losses along with \$21 million payment. It was handed back to China on July 1, 1997 - after 155 years.
- The second opium war (1853-1858) included Britain and France seeking for legalization of the opium trade and open ports with rights for foreign traders and missionaries to travel within China.
- US opium smugglers like John Astor and Franklin Delano Roosevelt's father made millions as "fair, honorable and legitimate trade". By 1818 the US provided 1/3rd of the opium to China.



Opium Use During the Civil War - Beginning of the First Opioid Crisis as a Wartime Medicine

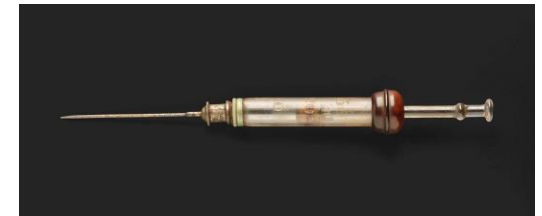


Opium pills, laudanum (mixture of opium and alcohol), and morphine injections were administered to soldiers with gunshot wounds, amputations and diarrhea. Countless veterans became addicted and continued after leaving the army.

The hollow needle used in hypodermic syringes was invented by Charles Gabriel Pravaz and Alexander Wood. Pravaz, a French surgeon, developed a syringe with a fine, hollow needle in 1851. However, it was Alexander Wood, a Scottish physician, who popularized the use of the hypodermic syringe for injecting medications directly into the skin. Wood's modification allowed for precise drug delivery and pain management, revolutionizing medical practice.

Civil War Union Army use:

- 10 million opium pills
- 2.8 million ounces of opium powders/tinctures



Addiction was termed “opium slavery” and “Morphine mania” with little sympathy or support. By 1888 Boston reported 15% of all prescriptions were opiates. Aspirin was not available until 1899.

Around 1900, heroin was briefly available through Sears & Roebuck catalog for \$1.50. It included two vials of heroin, a syringe, two needles and heroin-kit carrying case.

Why Has Fentanyl Replaced Heroin ?

No More Farming Poppy Fields!



Heroin versus Fentanyl Creation

Heroin was first synthesized in 1874 by an English chemist and promoted by the Bayer Company in 1898 as the *safer alternative* to morphine for pain and as a cough suppressant.

Steps to create heroin from opium

1. Need to grow the poppies and collect the latex from a hand cut seed pod
2. Extract the opium latex to isolate morphine by dissolving in water, filtering, and precipitate the morphine with acid.
3. Add acetic anhydride to create heroin
4. Purify and dry and package.

Steps to create fentanyl

1. Obtain 4-ANPP and reflux with propionyl chloride to create fentanyl.
2. Compounds are highly toxic and corrosive. Avoid water to prevent explosions!
3. One kilogram of 4-ANPP (\$800) can make 415,000 pills. Profit is 800 times cost of precursor chemicals. Street value of \$1.2 Million.



Fentanyl

- Fentanyl is an exceptional drug for the treatment of severe pain. I have used this post-operative severe pain, and it is wonderful! But severe limits are necessary for those in need to avoid addiction.
- The evolution of fentanyl abuse has become a national disaster and becoming worse each year with 70,000 people dying each year due to unexpected overdose, often from a purchased street tablet.
- There are TV reports daily of the deaths and millions of tablets seized. Many deaths are teenagers looking for fun on weekend looking for oxycodone or Xanax, which are contaminated or only contain fentanyl.
- Fentanyl is 100-fold stronger than morphine and 50-fold stronger than heroin.
- On May 7, 2024 we had the National Fentanyl Awareness Day.



Fentanyl Background

- Fentanyl was first synthesized in 1959 and used in healthcare since the 1960's for anesthesia, pain management, epidurals, obstetrics, etc. due to its potency and quick onset of action. Historically there was little medical staff abuse, however, now we are currently seeing a tremendous general public abuse as a street drug.
- It is relatively easy to manufacture which makes it an excellent illicit drug to produce and can be created in your garage. Heroin is created from extracted plant crop which take months to grow, harvest, and chemically create.
- Fentanyl is available as “lollipops”, buccal tables, sublingual tablets, sublingual sprays, nasal sprays, transdermal patches and injectables.
- In 2022 more than 131 million prescriptions were written opioids or 39.5 prescriptions per 100 persons.
- This down from 153 million prescriptions in 2019 or 46.8 opioid prescriptions per 100 people (CDC data).

Pill Press for Fentanyl Tablets

Anyone can make pills at home and the internet is filled with options from a single pill press to those capable of thousands of pills per hour.

It is easy to use and die presses can be bought to create the design intended and the compressible sugars bind the tablet together to dilute the active drug. Mixing appropriately is critical or the clandestine labs will create a “hot tablet” overdose.

In February 2024, the DEA finally sent a letter to the companies due to their failure to report equipment sales. eBay paid a \$59 million fine but you can still find them for sale.

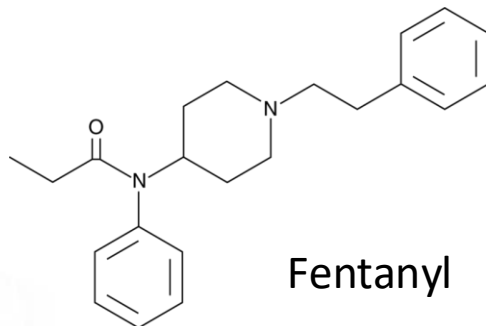
Pill Press for
\$450 on internet



Common Fentanyl's Both Medical and Illicit

Medical Fentanyl's

- Fentanyl
- Norfentanyl (metabolite)
- Alfentanil
- Remifentanil
- Sufentanil



Illicit Fentanyl's Examples (Total of 37)

- 4-ANPP (starting base chemical)
- Acrylfentanyl
- Carfentanil
- Cyclopropyl Fentanyl
- Flurobutyrylfentanyl
- Fluorofentanyl
- Furanyl Fentanyl
- 3-Methylfentanyl
- Methoxyacetylfentanyl



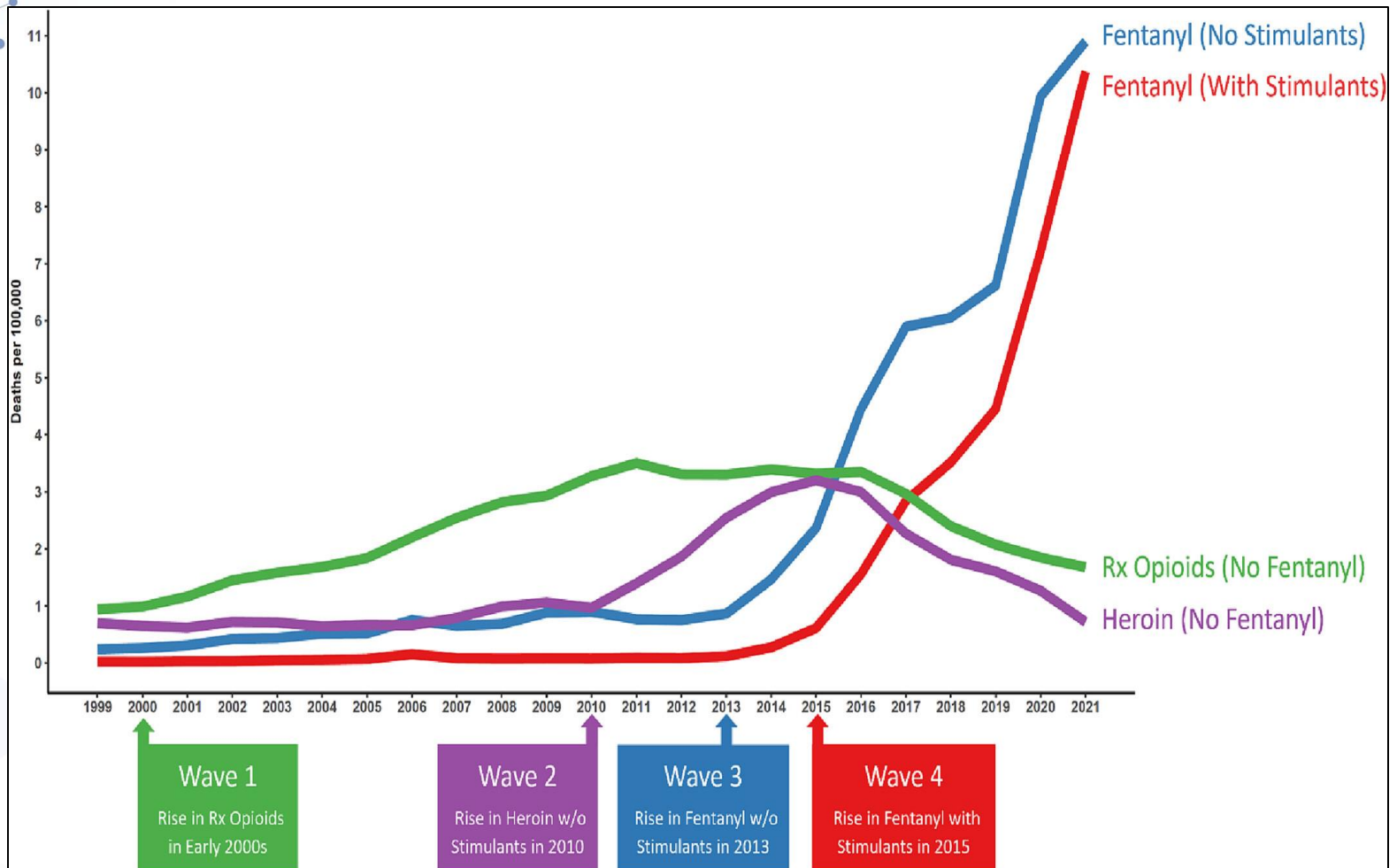
Moscow Theater Hostage Crisis: Fentanyl's First Use as a Military Drug and Mass Casualties

- Chechen terrorists seized the theater on October 23, 2002 and demanded that Russian forces to leave Chechnya.
- 40-50 terrorists took approximately 850-900 people hostage for three days and released some people each day but a negotiation for surrender was not possible.
- Rather than a military attack the decision was to gas the theater to subdue the terrorists.
- It was suspected that carfentanil and remifentanil were used to incapacitate the terrorists through the ventilation ductwork.
- However, the amount used was too high with 300 hostages reported killed due to overdose of gas.

Recent Waves of Opioid Overdose Deaths

- Wave #1
 - Started around 2000 with the rise in opioid prescriptions which resulted in “fake” pain clinics dispensing opioids in strip malls. Largely East and Southeast US initially.
- Wave #2
 - Rise in heroin deaths started in 2010 with the reduction in prescription opioid availability and manufacturing limits on hydrocodone and oxycodone.
- Wave #3
 - Rise in synthetic opioid overdose deaths in 2013 – primarily fentanyl.
 - More than 100,000 annual deaths with over 70% associated with fentanyl in street purchased pills or heroin use.
- Wave #4
 - Mixing of stimulants such as methamphetamine and cocaine with fentanyl or often referred to as “speedballing” began in 2015.
 - Since 2010 overdoses involving both stimulants and fentanyl have increased 50-fold and accounted for 32% of US overdoses in 2021.

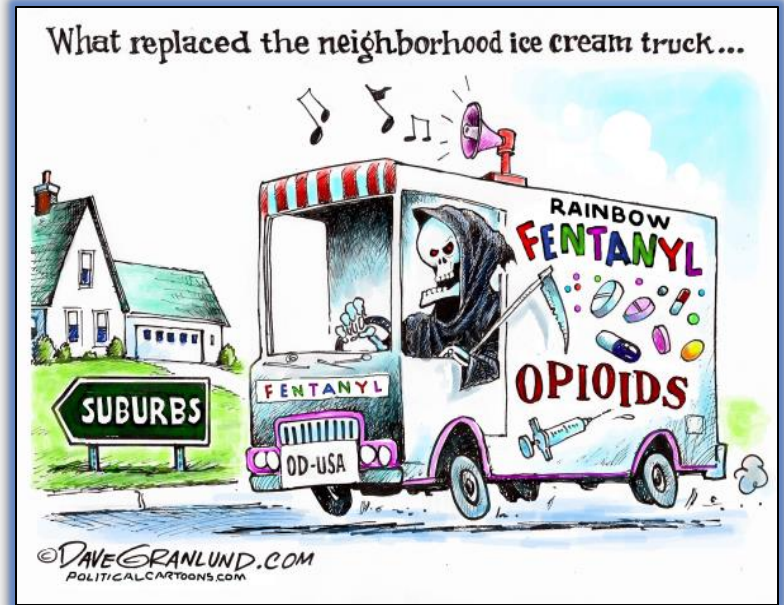
Four Waves of Opioids Abuse



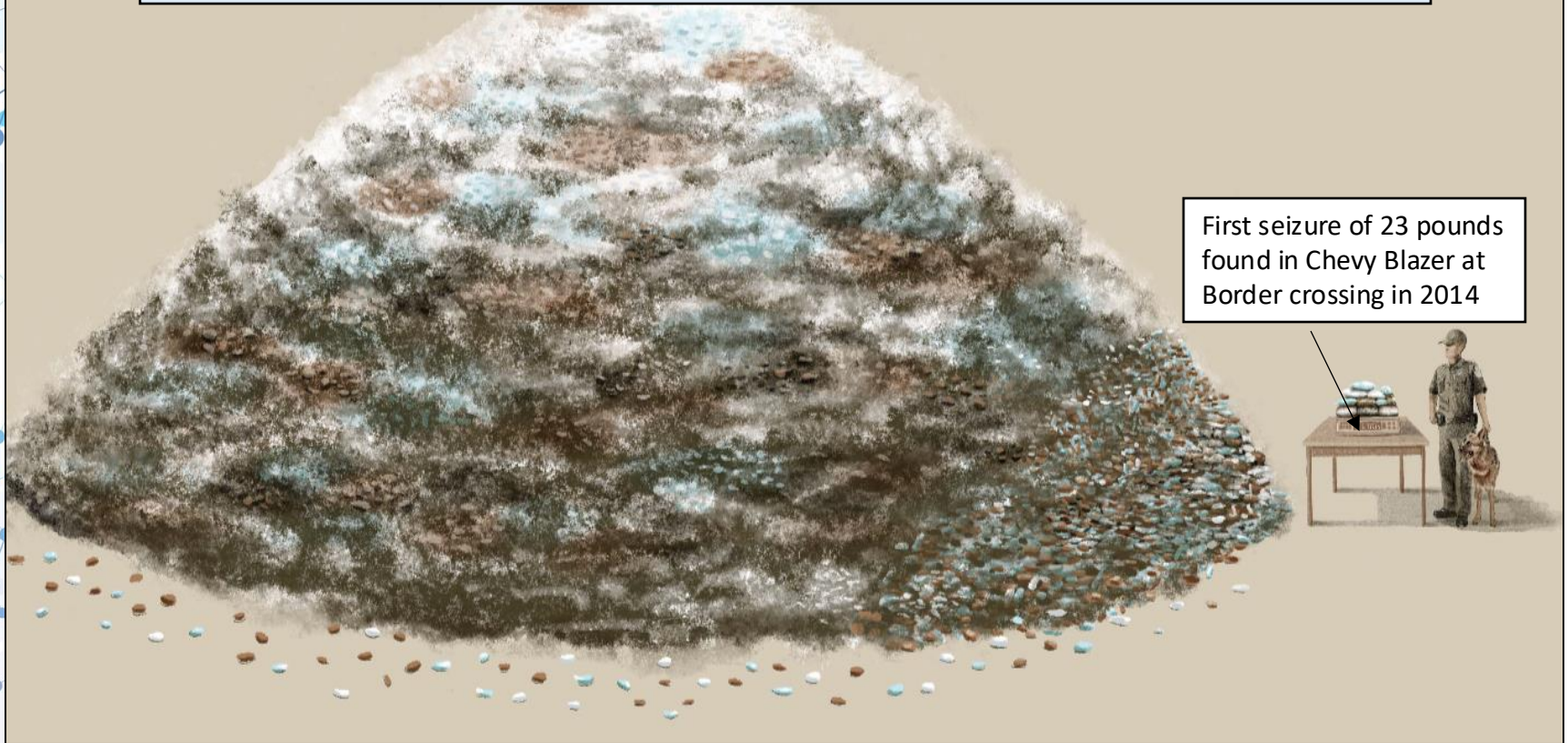
Friedman and Shover, 2023, doi: 10.1111/add.16318

Fentanyl and Analogs

- The #1 drug added to many illicit street drugs.
- Reports of more than 60% of pills bought on the street and found in combination with heroin or other drugs.
- Analogs have largely disappeared due to federal scheduling which makes the punishment the same as the illicit sale of fentanyl.
- The starter chemical for fentanyl is often 4-ANPP and largely comes from China and used to manufacture fentanyl in Mexico
- Latest development is to add xylazine or medetomidine for enhanced effects but is more deadly as Narcan is ineffective.



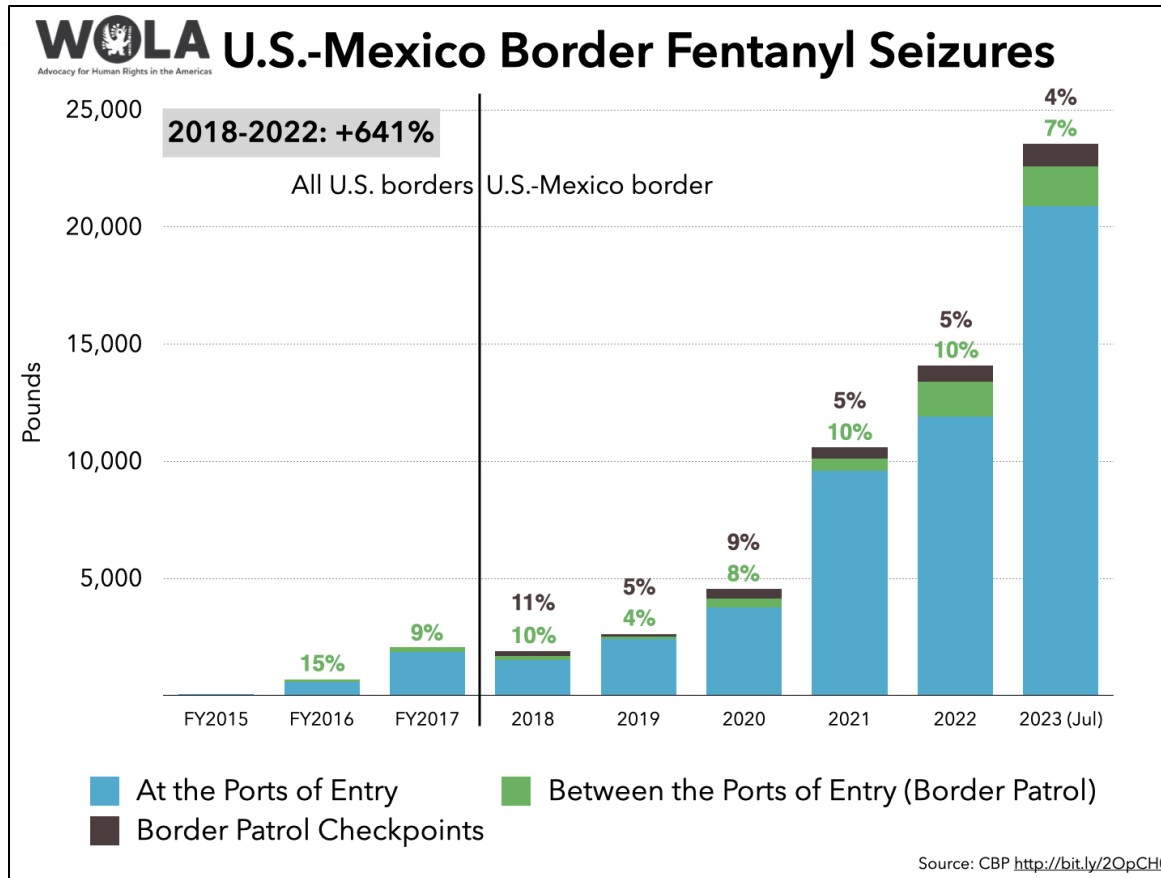
- ❑ In 2023 the DEA seized 79 million fake pills which represents 50 million deadly doses (23,700 pounds). Seized 33% more than 2022.
- ❑ 70% of pills had potentially deadly dose of fentanyl



First seizure of 23 pounds found in Chevy Blazer at Border crossing in 2014

Average seizure weight is 2.6 pounds.
20% of seizures are from pedestrians.
Only 7% of opioid seizures are heroin.

US Fentanyl Seizures



In a March 2024 report, the California National Guard seized 62,224 pounds of fentanyl in 2023. A 1066% increase over 2021. California seized more than 3 million pills already in 2024.

75,000 Fentanyl Deaths in 2023 - Falling Between Diabetes and Kidney Disease

Table. Number of Deaths and Age-Adjusted Rate of Deaths for Leading Causes of Death—US, 2019-2023^a

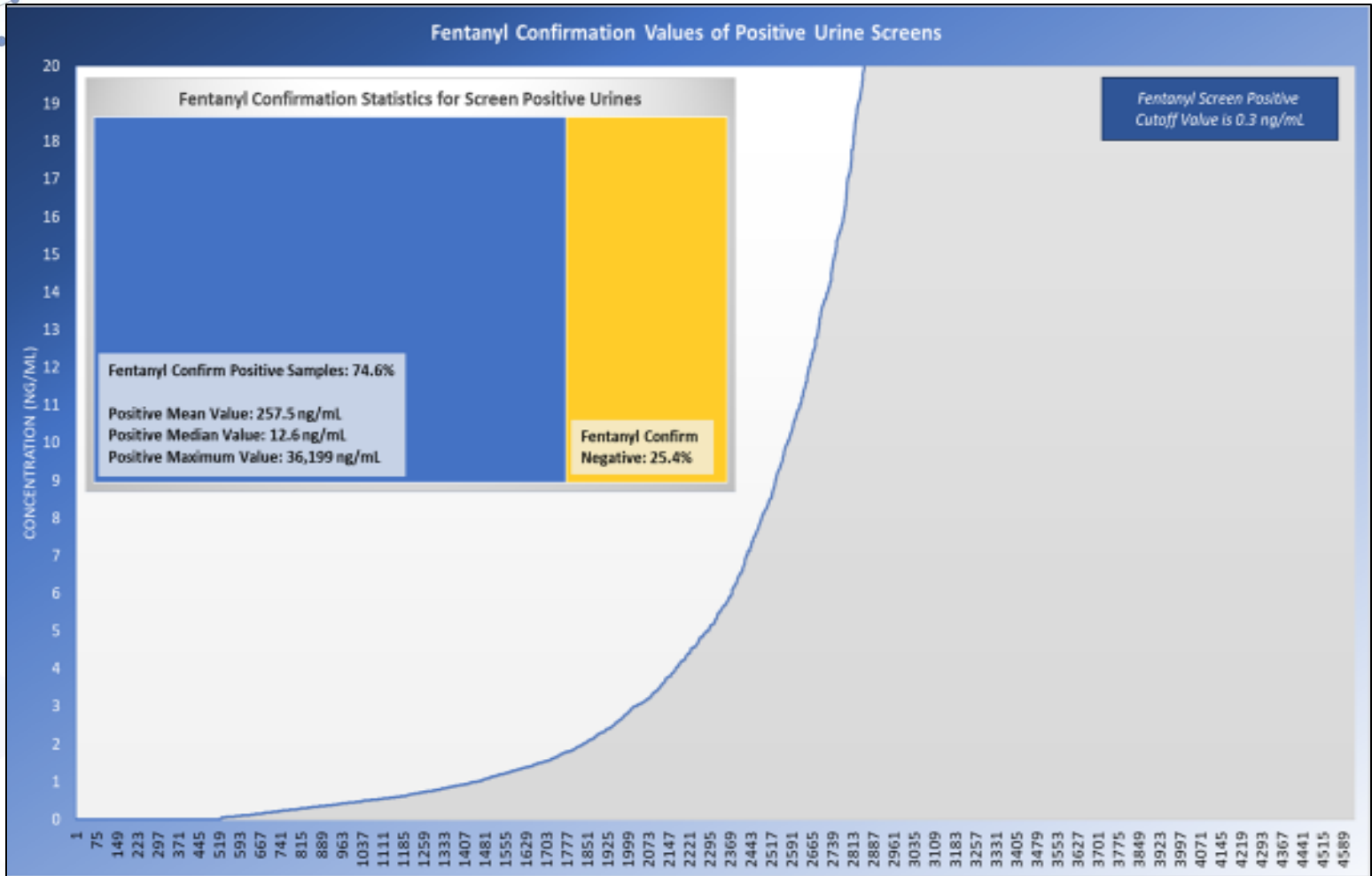
Underlying cause of death	No. of deaths (age-adjusted death rate per 100 000) ^b				
	2019	2020	2021	2022	2023
Total deaths	2 854 838 (715.2)	3 383 729 (835.4)	3 464 231 (879.7)	3 279 857 (798.8)	3 090 582 (750.4)
Heart disease	659 041 (161.5)	696 962 (168.2)	695 547 (173.8)	702 880 (167.2)	680 909 (162.1)
Cancer	599 601 (146.2)	602 350 (144.1)	605 213 (146.6)	608 371 (142.3)	613 331 (141.8)
Unintentional injuries	173 040 (49.3)	200 955 (57.6)	224 935 (64.7)	227 039 (64.0)	222 518 (62.3)
Stroke	150 005 (37.0)	160 264 (38.8)	162 890 (41.1)	165 393 (39.5)	162 639 (39.0)
Chronic lower respiratory diseases	156 979 (38.2)	152 657 (36.4)	142 342 (34.7)	147 382 (34.3)	145 350 (33.4)
Alzheimer disease	121 499 (29.8)	134 242 (32.4)	119 399 (31.0)	120 122 (28.9)	114 034 (27.8)
Diabetes	87 647 (21.6)	102 188 (24.8)	103 294 (25.4)	101 209 (24.1)	95 181 (22.4)
Kidney disease	51 565 (12.7)	52 547 (12.7)	54 358 (13.6)	57 937 (13.8)	55 250 (13.1)
Chronic liver disease and cirrhosis	44 358 (11.3)	51 642 (13.3)	56 585 (14.5)	54 803 (13.8)	52 220 (13.0)
COVID-19		350 831 (85.0)	416 893 (104.1)	186 552 (44.5)	49 928 (11.9)
Suicide	47 511 (13.9)	45 979 (13.5)	48 183 (14.1)	49 476 (14.2)	49 303 (14.1)
Influenza and pneumonia	49 783 (12.3)	53 544 (13.0)	41 917 (10.5)	47 052 (11.3)	45 182 (10.8)

^a Leading causes are classified according to underlying cause and are presented according to the number of deaths among US residents. For more information see Curtin et al.⁵

^b Data for 2019 through 2022 are final. Data for 2023 are provisional.

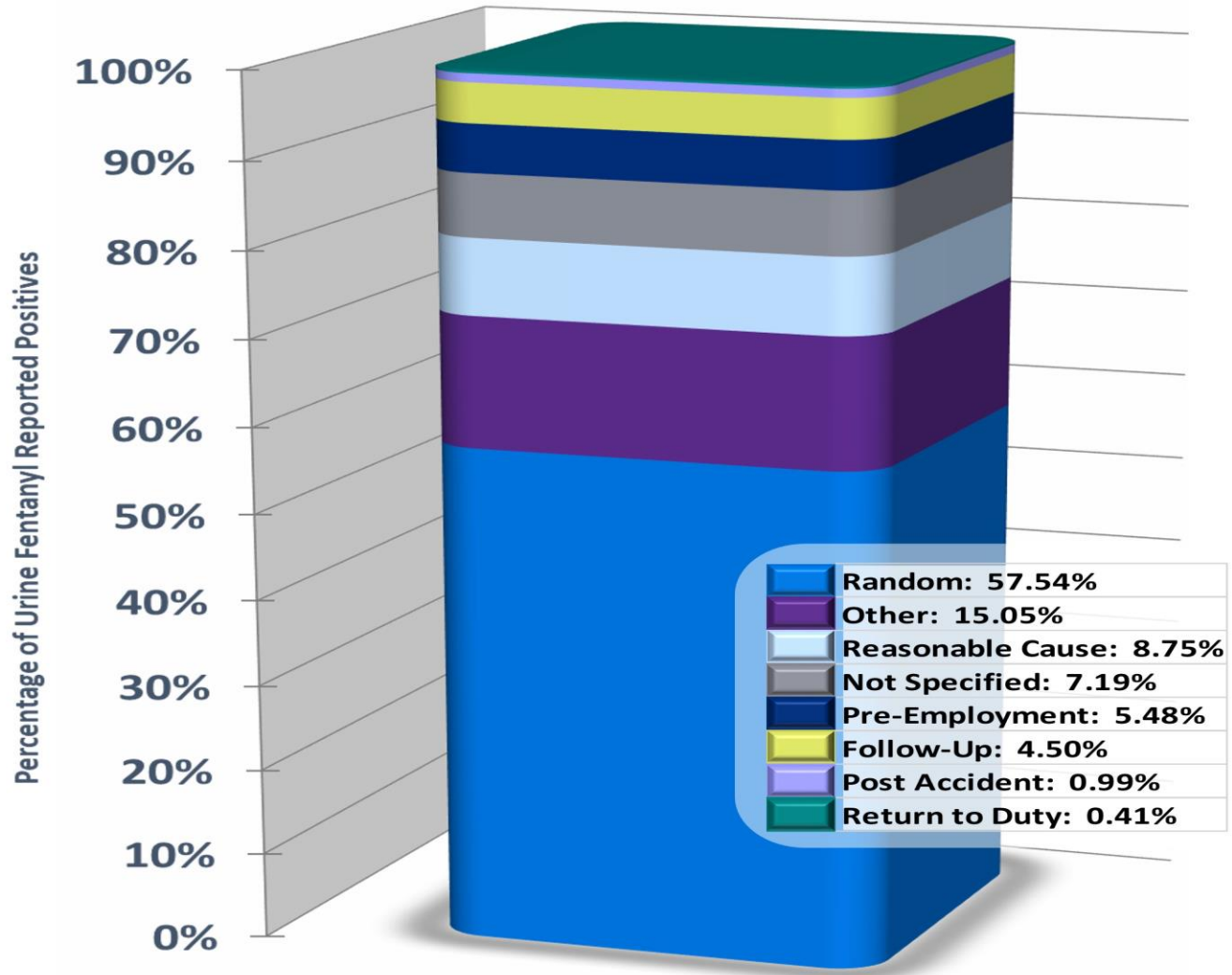
CDC reported Overdose deaths dropped 3% in 2023 compared to 2022 with 107,543 vs 111,029 deaths with over 1 million deaths since 1999.

Urine Levels of Fentanyl

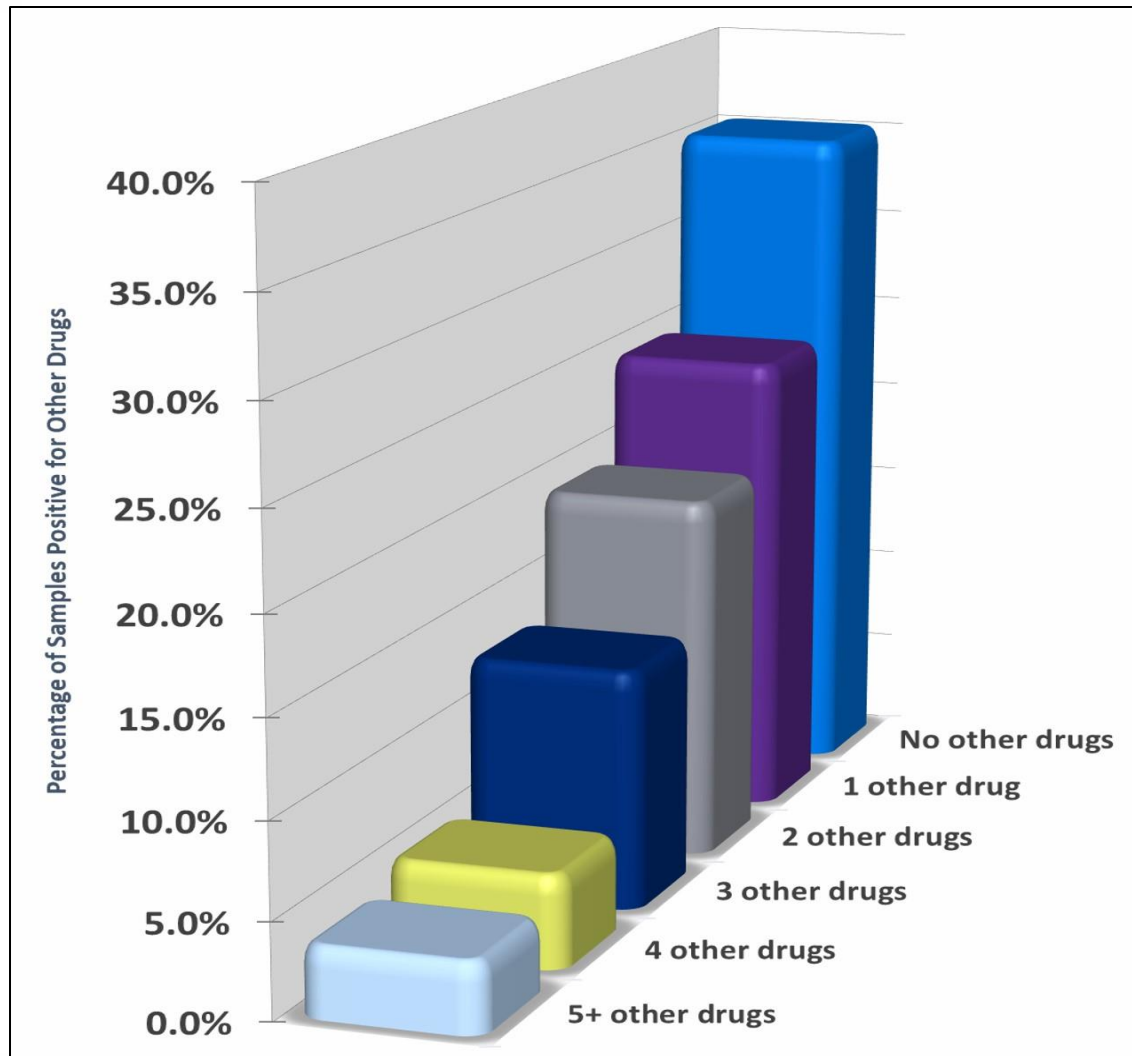


Fentanyl levels are 4-fold lower than Norfentanyl in urine!

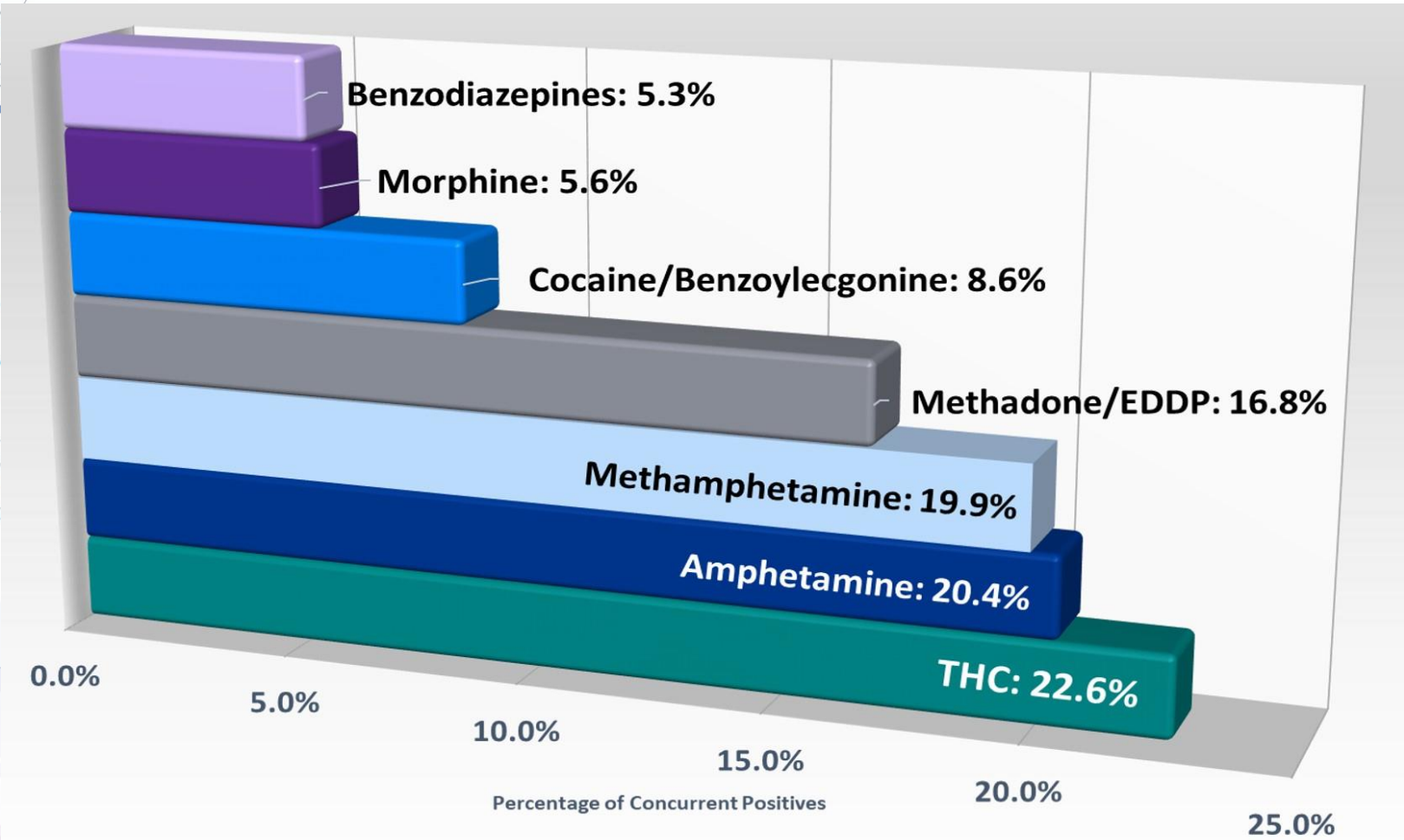
Fentanyl Positive by Test Reason - Urine



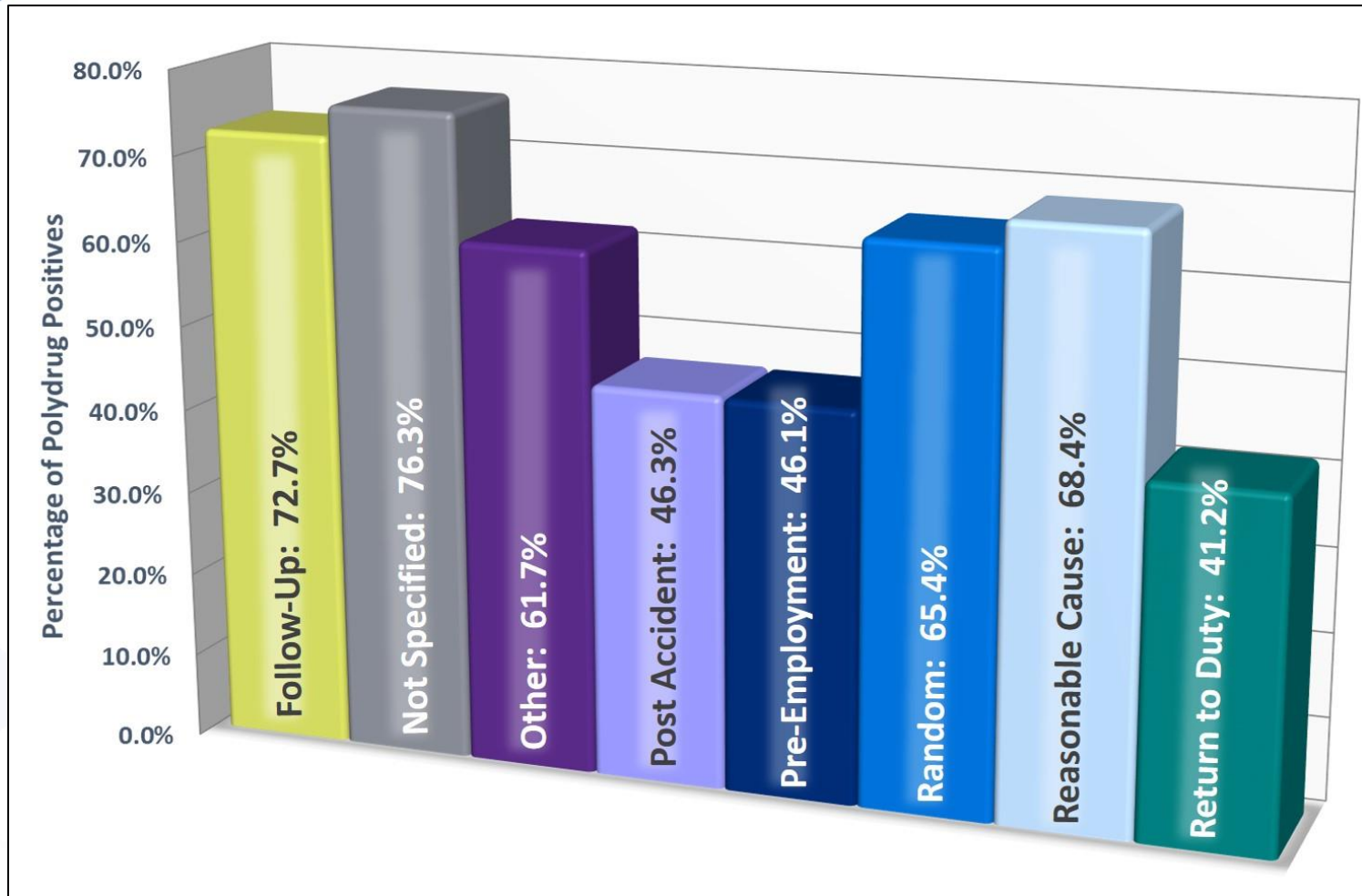
Fentanyl Concurrent Use With Other Drugs in Urine



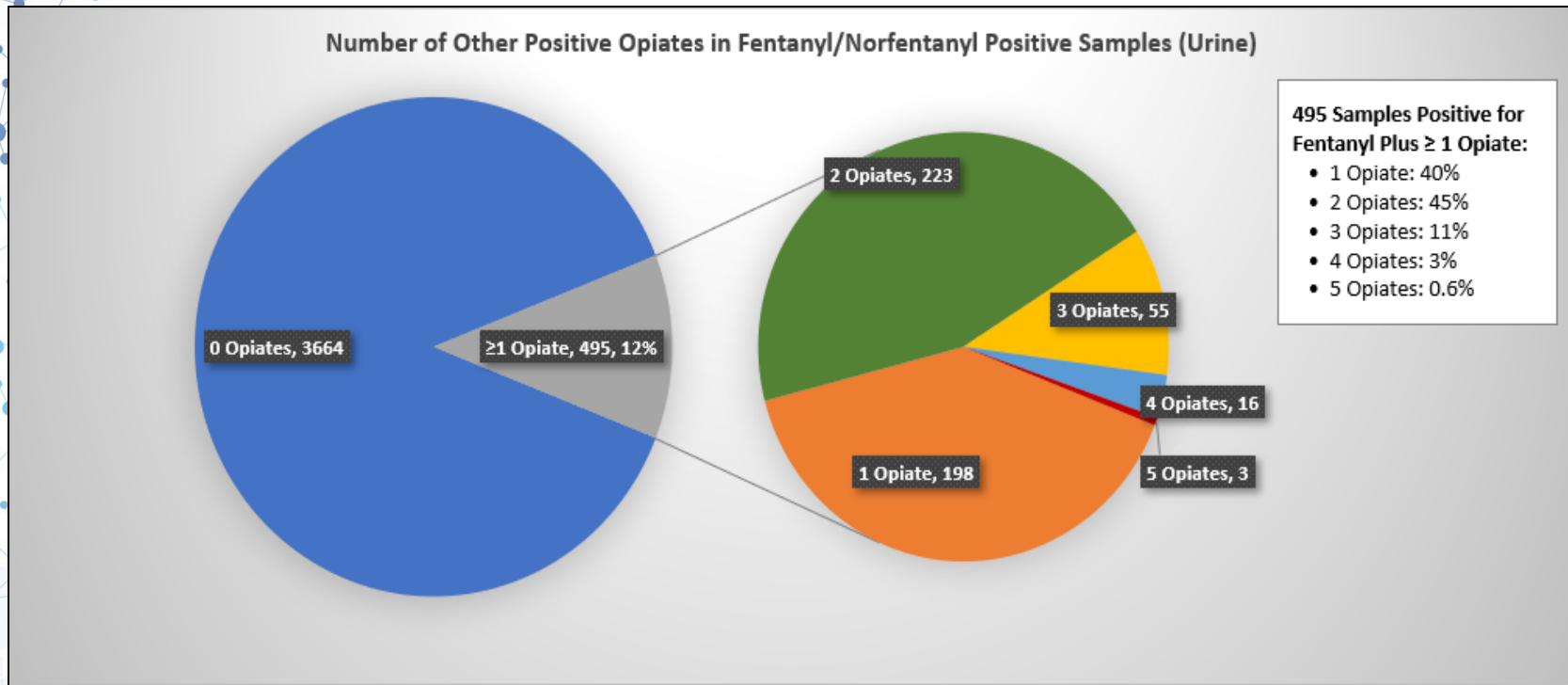
Fentanyl in Combination With Other Drugs in Urine



Fentanyl Polydrug Samples by Reason for Test

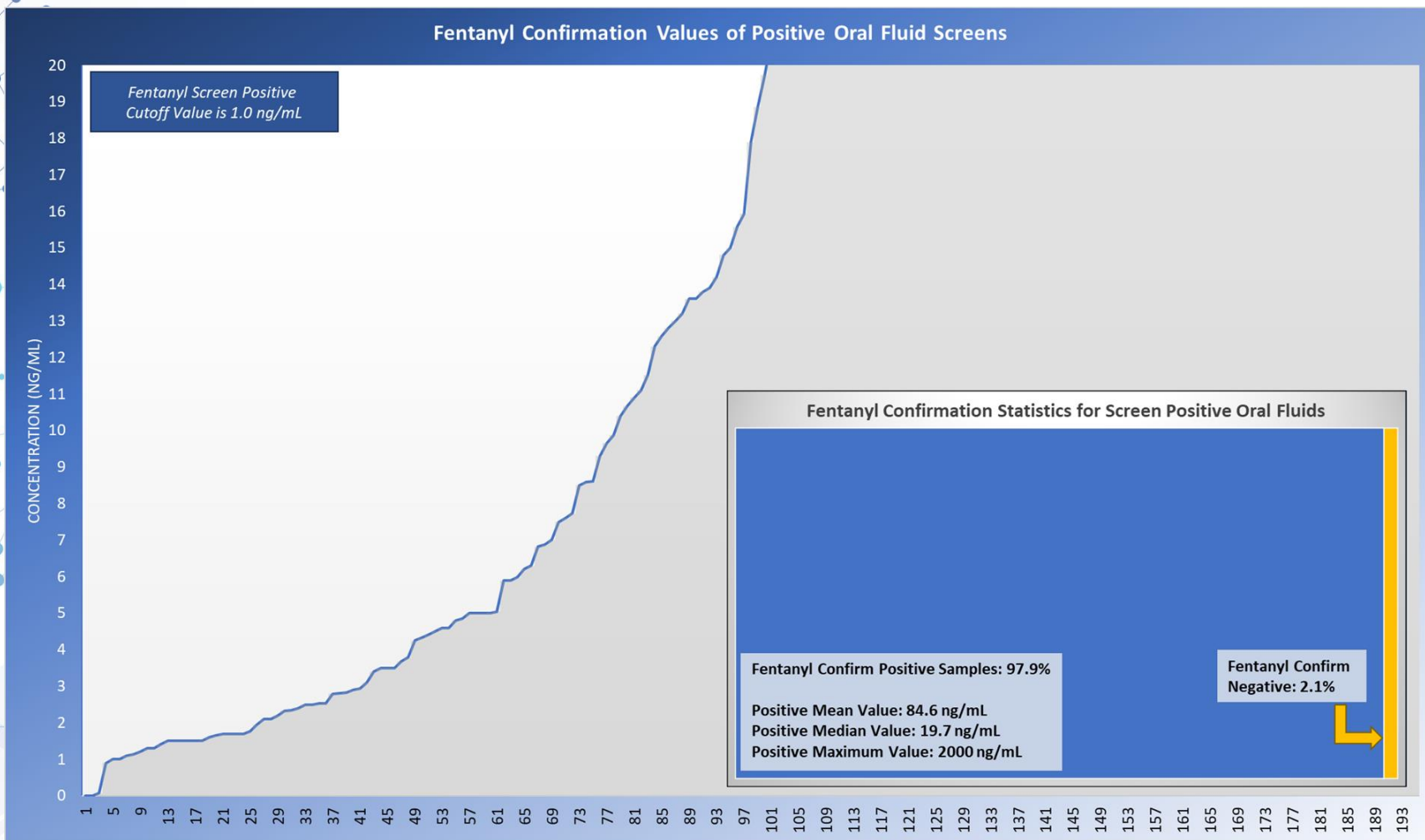


Urine Samples With Fentanyl and Opiates



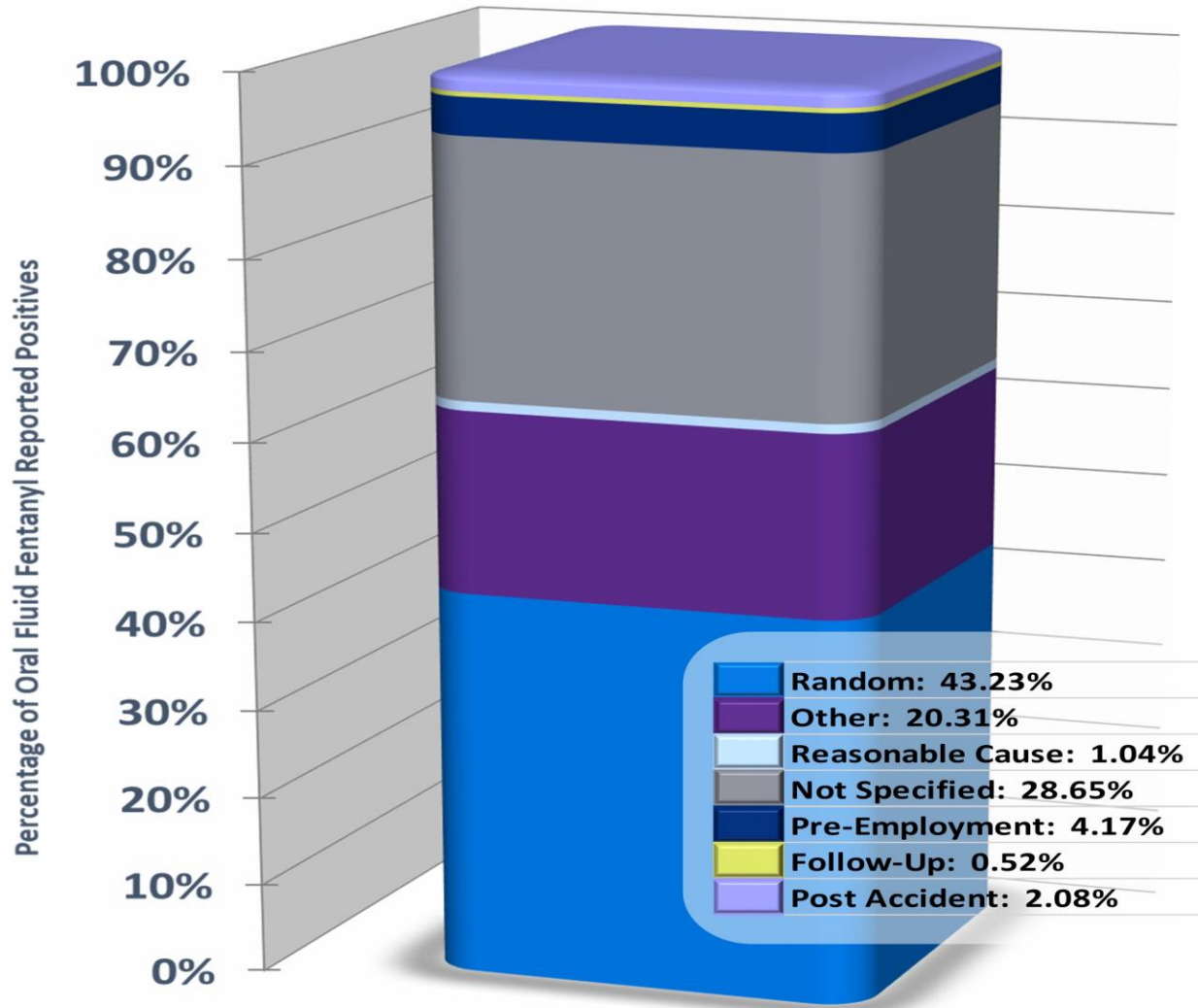
*Oral fluids are similar at 88 % without opiates present

Oral Fluid Fentanyl Levels

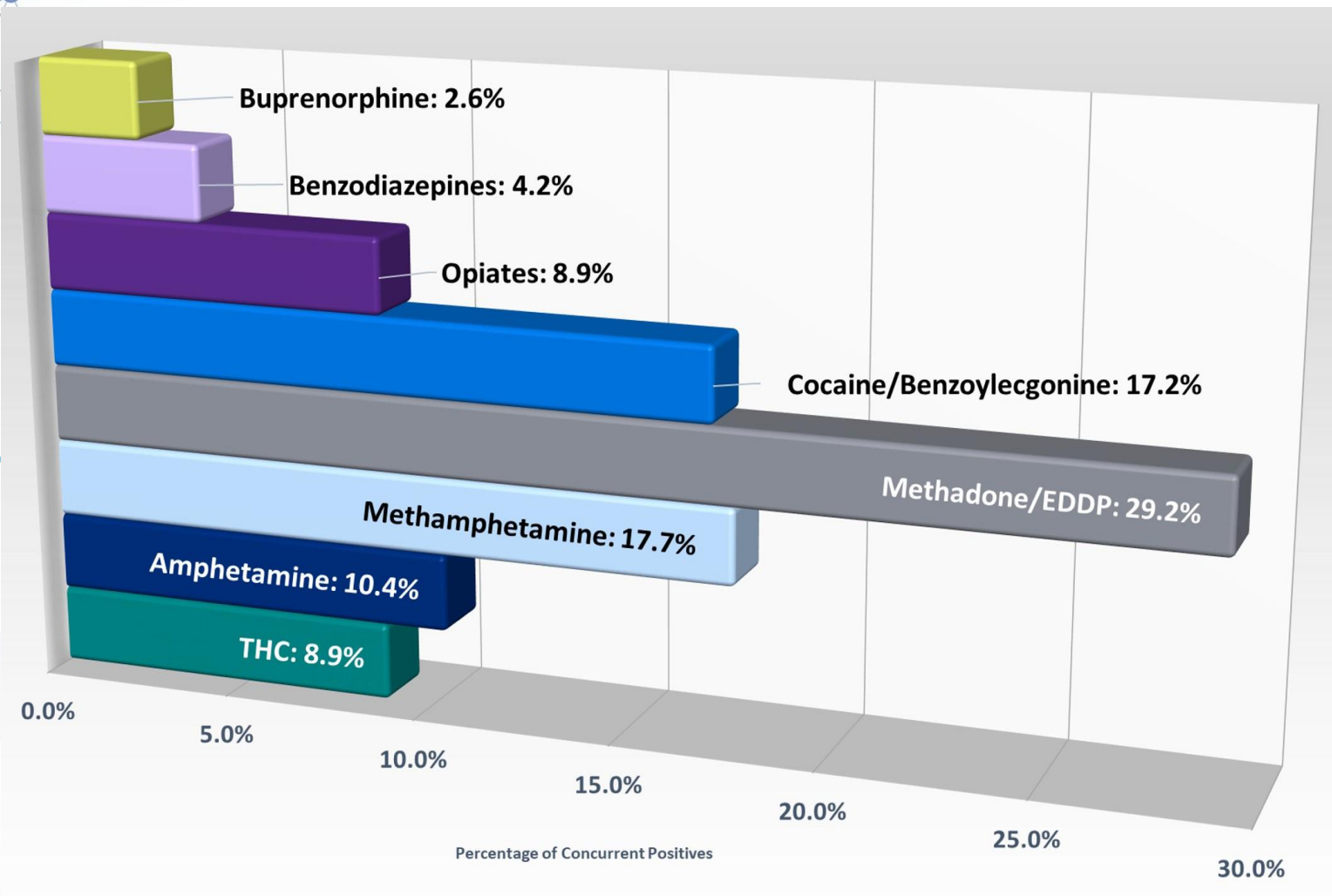


Fentanyl Levels are 5-fold higher than Norfentanyl in Oral Fluids!

Fentanyl Positive by Reason for Test – Oral Fluids

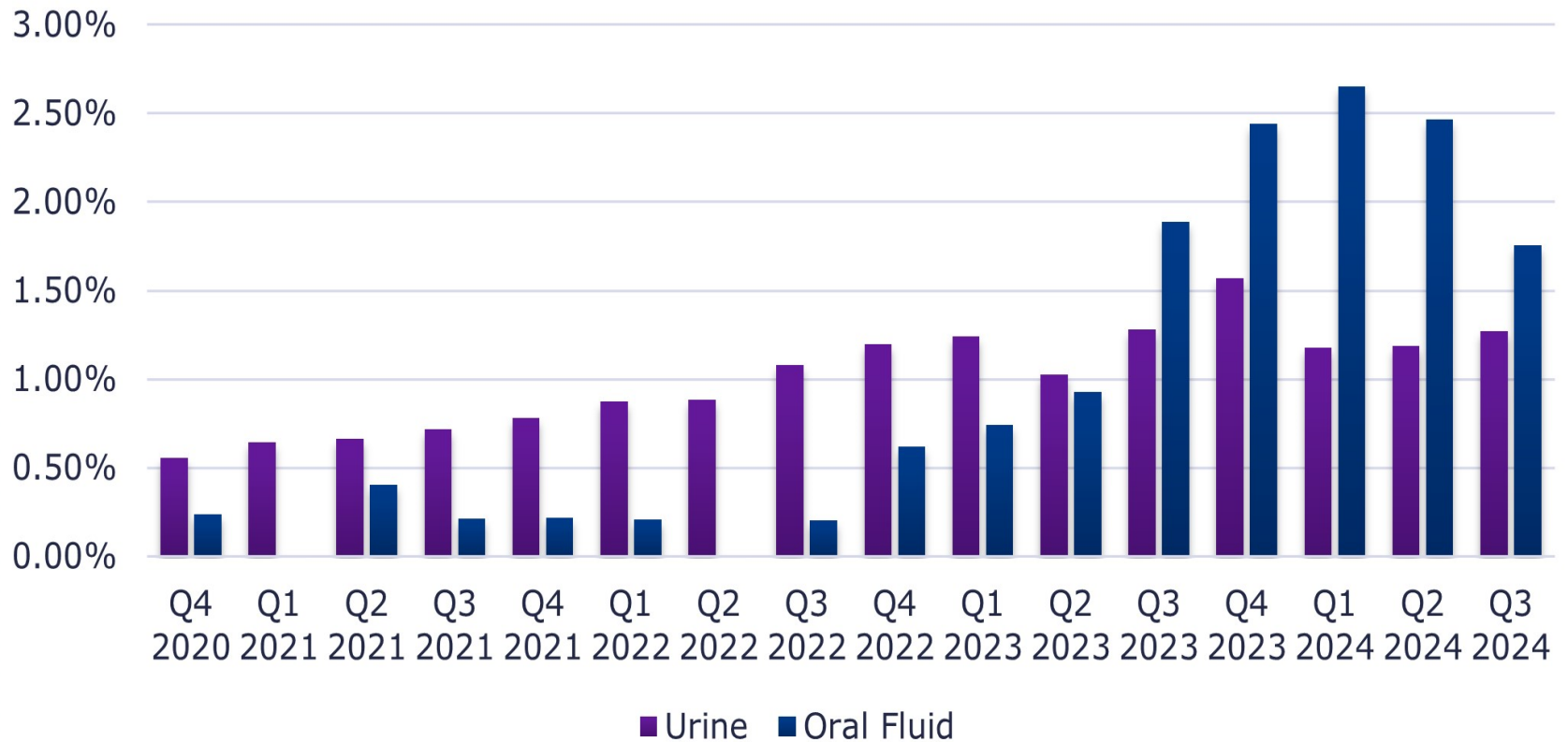


Common Oral Fluid Polydrug Positive with Fentanyl



Positivity Rate for Fentanyl in Urine and Oral Fluids

Workplace Fentanyl Positivity Rate



Quick Summary

- Opium abuse with foreign country trafficking had been around for several centuries to make money. A lot of money. The Mexican Cartels were not the first.
- Adding fentanyl to other drugs such as cocaine or methamphetamine seems to be popular with frequent overdoses with cocaine as it often snorted for an instant overdose.
- Fentanyl is not hard to identify in urine or oral fluids.
- Fentanyl is under review by HHS and DOT for future inclusion into the federal testing panel. But the urine and oral fluids must be in “lock step” for an eventual rollout. The timeline for inclusion is unknown.

Thank You
and Time for
Questions!

