

Episode 066:Fentanyl: The Next Phase in the Opiate Epidemic

by Amir Abuchaei and David Puder, M.D.



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**PSYCHIATRY &
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There are no conflicts of interest for this episode.

With the United States and the world transitioning to an era where pharmaceuticals and medications are mass produced, these bright opportunities to help the masses also pose some negative effects. The opioid epidemic fragments family units, with the loss of sons, daughters and parents. In this episode, we hope to educate people in the front lines about the third phase of the opiate crisis, namely fentanyl and its analogues.

What is Fentanyl?

The history of fentanyl had its foundation laid by Dr. Paul Janssen, who later came to be the founder of Janssen Pharmaceuticals, a company that in 2015 boasted an annual revenue of [\\$70.07 billion](#). During the early portions of his career, Janssen was looking to break out of the mold, set by his father, and to establish his own legacy. With his expertise in chemistry and with the help of a small donation, he synthesized one of the first formulations of fentanyl, and relatively quickly the drug gained success and notoriety.

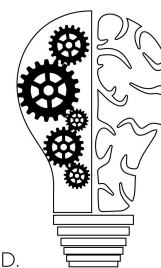
Fentanyl, a synthetic opioid, is primarily used for pain relief in various patient populations, namely those with breakthrough cancer pain, or with compromised kidney function, as the drug does not depend on renal clearance by the kidneys. Moreover, it can also be used for deep sedation prior to the initiation of a major procedure such as a coronary artery bypass graft. One surgeon interestingly remarked that this lengthy and life-saving procedure would not be possible without the creation of this drug.

Fentanyl, which was cheap to produce, provided physicians with another tool to curb pain. However, not much attention was given to this medication until the early 2000s.

Deaths due to Fentanyl Overdose: Why bring attention to it now?

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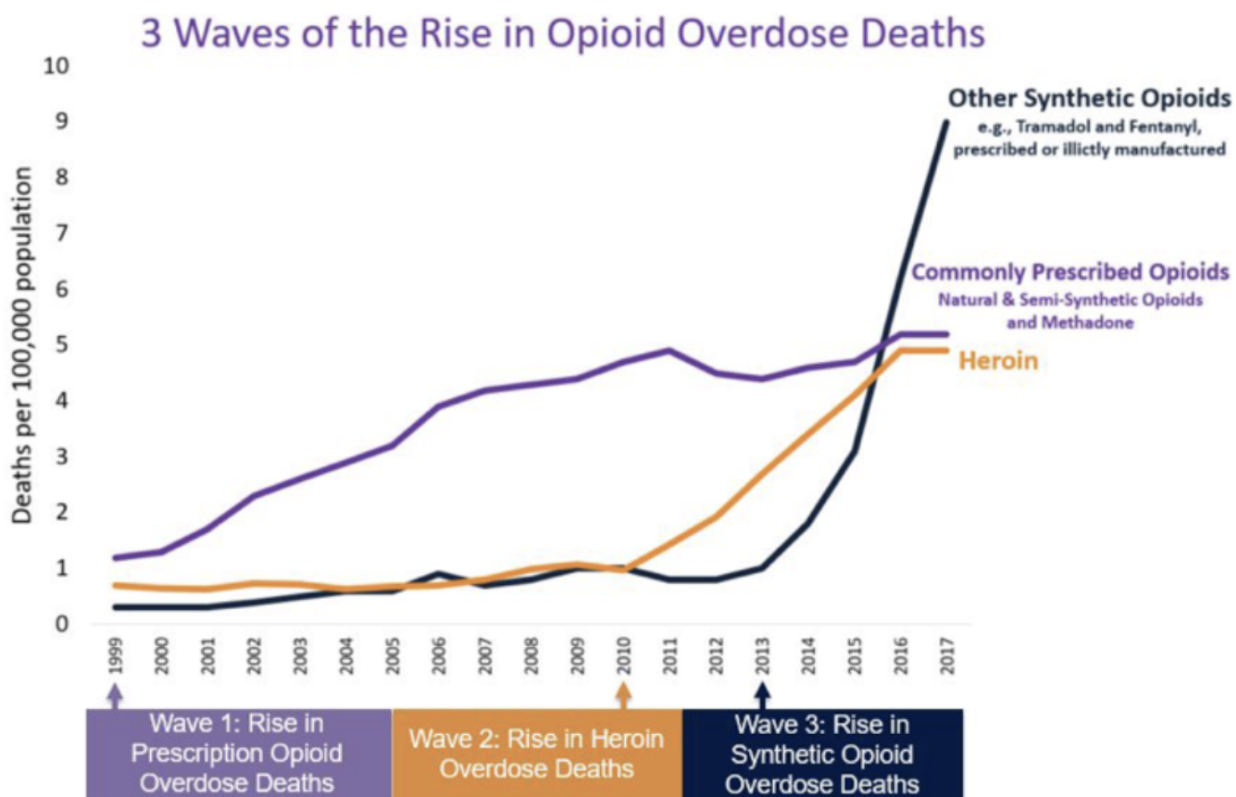
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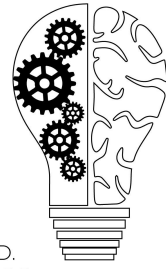
Deaths due to fentanyl are on the rise. According to [one CDC report](#), the rate of overdose deaths due to synthetic opioids increased **18% per year from 1999 to 2006**; this was met with a brief plateau, followed by an increase of **88% per year from 2013 to 2016**. Overall, there has been an increase in the overall number of deaths for those using opioids, both synthetic and natural, as well as heroin, however, it is remarkable to point out the significant rate at which synthetic opioid deaths have been increasing since 2013 and onwards.



In 2011 deaths due to fentanyl overdose were 1663; in 2016 they had skyrocketed to 18,335, an 1100% increase which was primarily seen in the 25-34 age group ([Spencer, 2019](#)). According to the director of the National Institute on Drug Abuse, Nora Volkow MD, substance users that are buying cocaine, heroin and even marijuana from the streets run the risk of their products being contaminated with fentanyl. Not only is this synthetic compound cheap to produce, it is also *easier* to produce, which creates more lucrative opportunities for manufacturers and dealers.

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With a product that not only has the same effect, but one that is much more potent, it is clear to see why there has been a rapid transition to it's more regular use.

In comparison to heroin, fentanyl can be mass produced in a small laboratory setting ([Mars et al., 2018](#)). This sets it apart from heroin, which requires large poppy fields, which run the risk of being destroyed and requiring time for recultivation and harvest. According to an article in [The Economist](#), 1 kg of fentanyl sells on the dark web for an estimated \$4,000, whereas heroin can be bought for \$6,000. The important part of this is that the fentanyl can be cut, processed, and sold for an estimated \$1.6 million, in comparison to a few hundred thousand for heroin. From a business standpoint, the choice is obvious.

Not only are overdoses occurring due to standard fentanyl abuse, but fentanyl analogs contribute to many deaths. Throughout the course of a year, 20.6% of deaths caused by opioid overdose tested positive for any fentanyl analog, and 11.2% tested positive for carfentanil ([O'Donnell et al., 2018](#)). Carfentanil, which is traditionally used for the sedation of large animals such as elephants, is the most potent analog known to man at the moment; reportedly 100 times more potent than traditional fentanyl, and 10,000 times as potent as morphine by weight. Only a few micrograms of this analog can lead to severe respiratory depression and subsequent death ([US National Library of Medicine, 2019](#)). That amount is approximately equivalent to **one** grain of sand.

Fentanyl in the Media: Celebrity Deaths

One could assume that illicit fentanyl would only affect those who would take the risk of buying products off the street, however, the current crisis extends into those who spend their time in the limelight. Before listing only but a few names, it should be noted that many [celebrity deaths](#) secondary to fentanyl have occurred in the early 2000s and onwards. This trend parallels the deaths that are occurring in the general public, which only heightens the speed at which attention must be brought to fentanyl.

Mac Miller, an American rapper, singer, and music producer passed away at 26 years old in 2018 due to fentanyl.

Lil Peep, an American rapper and singer passed away at 21 years old in 2017 due to fentanyl.

Prince, singer, and songwriter, 57 years old, passed away due to fentanyl.

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Tom Petty, fentanyl.

Domino Harvey, fentanyl.

The list goes on.

How is Fentanyl Purchased, Shipped, and Transported?

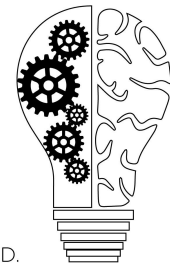
Illicit fentanyl is produced in strings of hard-to-identify laboratories in China. According to some reports, a majority of fentanyl that is exported is done so by a company that goes by the name of [Yuancheng](#). The company boasts an extensive product line, offering a selection of more than 11,000 drugs, ranging from anabolic steroids to fentanyl precursors. The authorities in China have had a tough time regulating the production and sale of not only fentanyl, but various other compounds as well. By the time authorities become aware of the specific analog and place it on a list of controlled substances, it is already too late, and chemists have already started synthesis of a compound with a tiny but significant change. They do so by adding small functional groups to the main compound to change the chemical structure and therefore avoid infringing with the law. However, as more and more groups are added to the core, the characteristic “high” that users experience begins to have unintended side effects and potentially lethal consequences ([Westhoff, 2019](#)).

The problem with addressing the transport and sale of illicit fentanyl is one of numbers and logistics, and at this time there does not appear to be a sufficient amount of funds and manpower to combat the export of fentanyl from China to the countries bordering the United States: Mexico and Canada. According to one spokesperson from the DEA, attempting to scan and interpret the contents of each and every package entering the United States is *logistically impossible*, even with the use of new technologies such as x-rays and the use of laser imaging. This problem is exacerbated when companies such as *Yuancheng* use simple yet effective techniques to hide the true contents of a package: for example, labeling a package of fentanyl precursor as containing “banana chips” ([Westhoff, 2019](#)).

How have the Chinese been so successful? How have these operations continued to move forward in China? In contrast to the [grotesque violence](#) carried out by drug cartels in South America with other cartels and occasionally publicized gunfights with the police, the opposite is seen in China. A combination of stringent gun laws and lack of violence makes draws less attention to the fentanyl trade. The Chinese have taken a different approach towards the drug trade, following the principle of *making money quietly*. Many of the chemical manufacturing companies in China are led by successful and low-key entrepreneurs who seek to attract as

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little attention as possible from authorities, and as of the writing of this article, this appears to be the formula for success ([Westhoff, 2019](#)).

Orders are placed online through the dark web; sites that cannot be accessed traditionally are done so via the use of a *Tor (Onion)* browser, which obfuscates traffic that is transmitted making it harder to identify the information being transferred. Payments are primarily made with bitcoin, one of the most commonly used forms of cryptocurrency, which deidentifies users, making it harder for organizations like the DEA to pinpoint who is ordering what. The process is so simple that 16 year old teenagers have the ability to do this, some being unaware of its potency and as a result, they overdose; others have noticed that they could turn out a large profit and have done so accordingly. One notable state that has seen a significant increase in overdose deaths is Ohio.

After the orders arrive in Mexico, cartels increase the weight of the purchased product (and therefore profits) by adding a variety of stabilizers and chemicals. The goal is to produce a similar effect as a prescription opioid for a fraction of the price with the intention of making a larger profit, or as one can say, “business.” After being pressed into fake tablets, the drugs are moved north of the border where they are distributed to users. What is important to point out is that many of the cartels mixing the fentanyl with these additives do so without the use of calibrated and sterilized equipment, instruments that you would find in a state-of-the-art laboratory ([Westhoff, 2019](#)). The margin of error is dramatically increased; a few extra micrograms of fentanyl can end someone’s life, and this is outlined in the paragraph below.

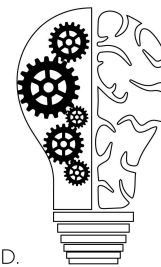
How does Fentanyl Kill People?

In comparison to other opioids, which may activate a variety of the opioid receptors, fentanyl has primary affinity for the mu opioid receptor ([Wood, 1982](#)). Activation of this receptor produces the effects that are commonly seen when consuming opioids, such as a decrease in pain perception, pupillary constriction, and respiratory depression. When discussing the pharmacokinetics of fentanyl, it’s lipophilic nature allows for quick association and dissociation from not only receptor sites, but also the bloodstream; duration of action for fentanyl is estimated to be 30-60 minutes total, whereas in heroin it is a total of 4-5 hours. This is what makes fentanyl so dangerous.

During a typical heroin overdose, emergency responders commonly have anywhere from 20-30 minutes to respond and administer naloxone ([Darke, 2016](#)). This response window is decreased to 2-3 minutes in fentanyl overdose ([Green, 2016](#)). This is not an appropriate amount of time for medical services to arrive before a user has succumbed to the effects of hypoxia.

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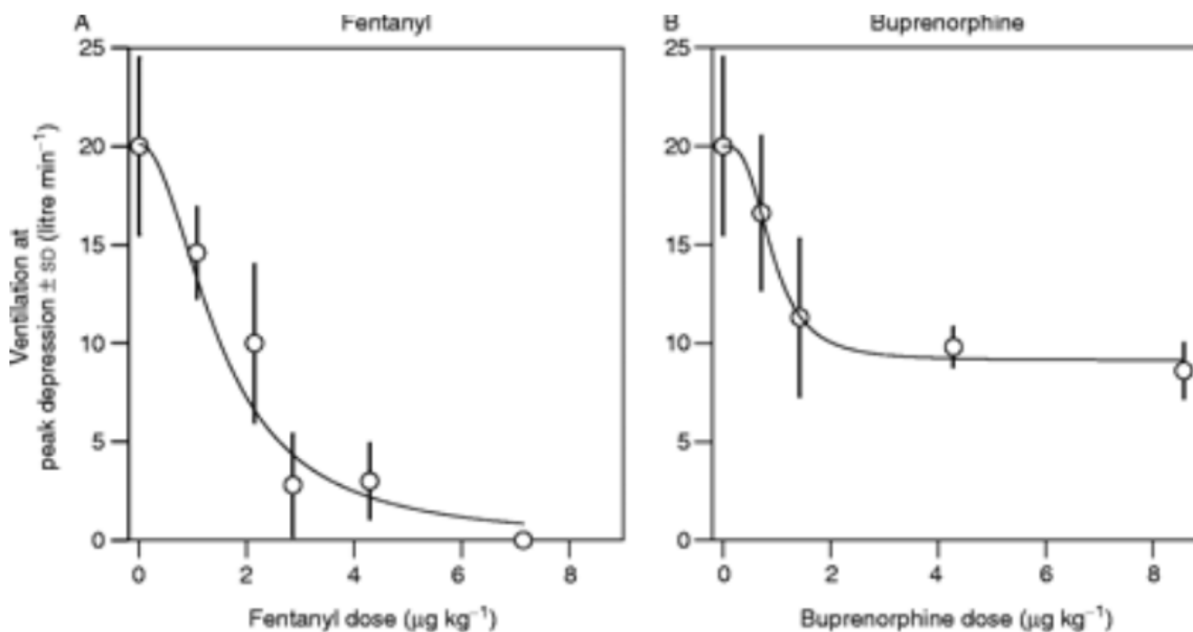
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The relatively narrow therapeutic index of fentanyl makes it so that even minute increases (measured in micrograms) can cause a significant change in respiratory function. A study investigating the comparison of dose-dependent respiratory depression of fentanyl vs. buprenorphine demonstrated the following: 1) Fentanyl-induced, dose-dependent depression of ventilation was seen when doses exceeded 2.9 micrograms/kilogram. As doses approached 7 micrograms/kilogram, patients were seen to approach apneic levels within 2-3 minutes. There was a clear dose-response relationship when concentrations were increased ($p < 0.001$). 2) In comparison, even at similar and greater concentrations of buprenorphine, the greatest respiratory depression was also seen but maximum potency was viewed with a ~50% reduction ($p < 0.001$). This highlights how small changes in fentanyl dosing can produce unintended effects ([Dahan et al., 2005](#)).

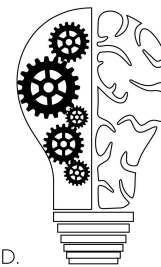


How is Fentanyl Overdose addressed?

In a suspected overdose, EMS only has minutes to respond. The main medication that is used is Naloxone, also known as *Narcan*. It can be administered in 4mg doses intranasally; there are also intramuscular injections available at 0.4mg. Few studies have been conducted that analyze the pharmacokinetics of naloxone for opioid overdose reversal. More importantly, EMS and healthcare practitioners would ideally prefer to use a more bioavailable form of naloxone that can reverse overdose symptoms more quickly. According to one study, the time to peak plasma

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concentration of naloxone did not differ significantly when comparing the IM and IN formulations ([Krieter et al., 2016](#)). In addition, the time to reversal of opioid overdoses has been similar with both forms of administration ([Kelly et al., 2005](#)). It is suggested that the main limitation to IN naloxone is occlusion, preventing the medication from reaching it's anticipated target located within the nasal mucosa. This is but another obstacle that makes the job of EMS more difficult in the field ([Barton et al., 2002](#)).

Another question that requires further elucidation: How *much* naloxone is required in a standard fentanyl overdose? Or carfentanil overdose? At this time there have been very few studies regarding this topic. One study conducted in Cook County identified a variety of dosages of Naloxone to reverse the effects, but one theme was clear: multiple doses were required. One unresponsive patient required 12mg of naloxone, that's **30 times** the standard dose to reverse the overdose, with two other patients requiring 8mg and 6mg, respectively. In this particular study, only about 15% of the cases arriving in the ED had fentanyl OD reversed with one standard dose (0.4mg) of naloxone ([Schumann et al., 2008](#)).

When considering studies such as this one, it is important to take a few things into account:

- 1) The cost associated with reversing overdose, some smaller community hospitals may not have adequate resources to administer such quantities.
- 2) Education: A recent public health advisory addressed by the US Surgeon General emphasized the importance of [understanding how to use Narcan](#). Moreover, whereas Narcan can cost \$130-140 per kit with two doses, the generic version can be bought for \$20-40 per dose. There are public programs that offer free naloxone for some drug users, however, these vary on a state to state basis and some patients have told me that naloxone makes their friends more bold to use higher doses of drugs. The problem then falls into the hands of local state agencies to establish working relationships with community leaders and more importantly pharmaceutical companies; the goal being to improve both of these modalities.

Conclusions:

The opioid epidemic appears to be making a rapid shift towards synthetic drugs as more potent and deadly options have become available during the last 20 years. This, in combination with foreign (and local) desires to make money, has only worsened the issue. In conclusion, the highlights of this post are as follows:

- China continues to be at the forefront of fentanyl exporters which floods the US market

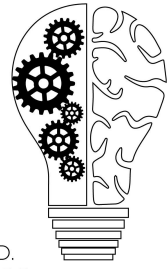
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- Overdose deaths have significantly increased during the mid-2010 era, and can be projected to continue increasing into 2020s and onwards
- Fentanyl overdose are affecting American citizens from all socioeconomic statuses

Solutions:

We can consider the power of detox followed by partial (day treatment) programs. At the institution where I work, we have one for chronic pain, dual diagnosis and more pure chemical dependency issues. Intensive therapy after detox provides one potential pathway out of drugs because it gives time for new coping skills to be formed and trauma to be worked through. Other potential options include methadone or suboxone maintenance. Although expensive, a long acting naltrexone that is injectable can also be used monthly. Future treatments may include a [fentanyl vaccination](#), however, at this time this is a proof of concept and additional time would be required to translate the results to humans.



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