

The Role of Synthetic Opioids in the U.S. Opioid Crisis

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Abstract: The United States Department of Health and Human Services officially declared the ongoing opioid crisis a public health emergency in 2017. Due to the increasing over prescription of opioids for pain relief, the production of illicit alternatives, and the broken American healthcare system that could not prevent the spread of the opioid epidemic, the U.S. saw a constant, rapid surge of deaths from opioid overdoses. These opioids include a variety of commonly prescribed medications, but recent data and cases indicate that synthetic opioids are becoming the main contributor to these fatal overdoses. Synthetic opioids such as fentanyl are approved for medical purposes due to their designed potent properties for pain relief but are often misused due to false marketing by pharmaceutical companies that it produces a “safe and legal high.” Its potent properties are what get victims easily addicted and hence fatally overdose. This paper analyzes the role of synthetic opioids, specifically fentanyl and fentanyl analogs, and how it has shaped the opioid crisis and American public health.

Keywords: opioids, drugs, synthetic opioids, drug crisis, drug epidemic, fentanyl, public health.

I. INTRODUCTION

Although the deadly consequences of opioids seem to have only been highlighted by the recent opioid crisis, the history of opioid use dates back to ancient civilizations. Opioids have been in constant use for general pain relief, anesthesia, or recreationally used by civilians for their euphoric properties. However, as corrupt pharmaceutical companies began to capitalize on opioids and aggressively market them to doctors for use, the healthcare system has failed to contain the opioid crisis and the many contributing health disparities. Due to the overprescription of opioids and the increasingly accessible black market, there has been a surge of opioid overdoses leading to fatality. Due to the increasing number of overdoses involving opioids, the U.S. Department of Health and Human Services officially declared the opioid crisis a public health emergency in 2017 and continues to renew this determination in 2023¹.

Synthetic opioids are major contributors to the increasing number of deaths in the United States caused by opioid overdoses, often associated with the third wave of the opioid overdose epidemic that began in 2013². According to data from CDC, synthetic opioids have been responsible for the most deaths of any type of opioid, accounting for more than 82% of all opioid-involved deaths and being involved in increased death rates by 56% from 2019 to 2020². Synthetic drugs are often marketed by manufacturers in that they provide a “legal and safe high” for which victims fall addicted to their potent high³. However, this is not true as they are synthesized in the laboratory to have more potent effects than morphine and heroin, hence increasing their addictive properties, which makes them more prone to abuse and result in fatal overdoses. Most synthetic opioids circulating in the United States are synthesized abroad and aggressively imported into the US market, making this a wider international issue⁴.

II. EVOLUTION OF OPIOID USE

The use of opium traces back to as early as 3000 B.C. when ancient Sumerians cultivated the opium poppy as a euphoriant limited to religious ceremonies⁵. Clay tablets from ancient societies have a record of extracting opium from the flowers, but the exact origin of opium’s use for pain is not known⁵. However, as opium became increasingly popular for its medicinal and recreational purposes, traders distributed and introduced opium throughout Eurasia from the Egyptians to the Chinese⁵.

Although there was some taboo about its use, opium was commonly smoked by civilians, many of whom did not know that opium was a depressant drug with potential dangers⁵. With its deep history, opium became widely used as general pain medicine, as it was prescribed for various conditions throughout the 19th century. During the Civil War in the 1860s, these opioids, especially morphine, were used to treat wounded soldiers for pain⁶. This started a modern generation of addicted veterans and heavy dependence on opioids in medical care.

However, instead of improving these situations, the healthcare system failed to support this addiction and instead fueled it to gain profit. Some pharmaceutical companies began using this rising trend of opioids to come out with even more addictive products. This is represented by the first wave of the opioid overdose epidemic, beginning with the increased prescribing of opioids². The faults of the pharmaceutical industry's role in this epidemic are highlighted by the crimes of Purdue Pharma, infamous through their best-selling OxyContin, also known as oxycodone⁶. Initially marketing it as a more gentle and less-addictive opioid, doctors began to prescribe Oxycontin to patients for pain relief as it was an easy alternative to other treatments or therapies⁶.

Especially after the American Pain Society campaigned for "pain as the fifth vital sign" in 1995, doctors began to resort to only prescribing pain-killing opioids for pain treatment instead of seeking other alternatives⁷. Although this campaign intended to encourage proper evaluation and treatment of pain, physicians relied more on easily accessible opioid analgesics, which also helped with the reduced federal healthcare funds⁷. However, the opioids' potent properties weren't as well known due to aggressive, false marketing by pharmaceutical companies such as Purdue Pharma, which encouraged medical professionals to trust the medications. As more and more patients fell victim to this highly addictive yet legal painkiller, there have been increased cases of opioid addiction, misuse, abuse, and overdoses, often leading to tragic deaths.

Despite regulations and lawsuits against Purdue Pharma and other potential threats, opioids continued to be heavily prescribed, contributing to the ever-increasing number of addicts and deaths by opioid overdose⁶. This epidemic started decades ago, and we only realize now that it has spread throughout America from coast to coast. Interestingly, certain regions have been especially hit by the opioid epidemic, notably Appalachia, which has markedly higher poisoning mortality rates from both pharmaceutical and illicit medication abuse⁸. Analyzed factors include "higher rates of injury-prone employment, aggressive marketing of prescription pain medications to physicians, and an insufficient supply of behavioral and public health services targeting opioid misuse"⁸. Appalachian communities also generally have high poverty rates, contributing to limited access to proper treatment.

Due to all these factors, opioids have evolved from a widely used medical product to a highly addictive drug. In more economically disadvantaged areas where people did not have supportive health services, users addicted to the highly marketed prescription opioids turned to illegal alternatives to abuse again. The illicit alternatives were produced locally by underground drug-makers who designed these modified chemicals to make them legal to sell and lower costs⁹. Because these drugs are synthesized, they can pass through standard drug tests and evade manufacturing policy restrictions and laws⁹. In addition, a culture of international drug trafficking systems and black-market drug dealers arose, further increasing the number of overdoses and illegal misuse of these drugs.

III. WHAT ARE SYNTHETIC OPIOIDS?

Natural opioids, called opiates, are natural substances extracted from the opium poppy plants, which include morphine and codeine. Synthetic opioids, as the name implies, are human-made chemicals manufactured in the laboratory. Chemists purposely modify the original structures to design synthetic opioids to act on the brain similar to natural opioids, often to make their pain relief abilities become more potent.

To explain the science behind these opioids, the molecules of the chemicals are receptor agonists that selectively bind to opioid receptors, hence inducing a biological response¹⁰. Despite the different chemical structures, synthetic opioids mimic natural opioids by binding to and activating opioid receptors on the surfaces of nerve cells in the brain¹⁰. When opioid receptors are activated, the response pathway of the linkage triggers the brain's reward system and releases dopamine, which stimulates feelings of pleasure. In this way, opioids can temporarily mimic natural endorphins that relieve pain by blocking pain messages from the body and spinal cord to the brain¹⁰.

This pathological response has been proven to be even more exaggerated with synthetic opioids, which leads to higher addiction rates. Synthetic opioid molecules also activate opioid receptors inside nerve cells, specifically in the Golgi apparatus where natural endogenous molecules can't reach¹⁰. This indicates that synthetic opioids could pass through cell membranes without binding to special receptors or going through endosomes, hence reaching their target much quicker than

endogenous molecules¹⁰. This difference in that synthetic opioids can take effect much faster contributes to the higher addictive potential of these opioid drugs¹⁰. Especially as the body becomes accustomed to the drugs and their ability to block pain, drug users end up using higher dosages to fulfill their addiction to that feeling of high⁶.

IV. FENTANYL

Fentanyl is a synthetic opioid with the chemical formula of $C_{22}H_{28}N_2O$ that is medically used for pain relief. However, behind this combination of the familiar elements of carbon, hydrogen, oxygen, and nitrogen is a highly potent synthetic drug that is said to be fifty to a hundred times stronger than morphine and heroin¹¹. Fentanyl was developed in 1959 by Dr. Paul Janssen of Janssen Pharmaceuticals as an intravenous surgical anesthetic and analgesic, hence clinically approved for treating severe pain¹². Since the 1960s, fentanyl has been playing an important medical role in managing chronic pain for patients who aren't as responsive to weaker analgesics. However, fentanyl's "quick duration of action" that provides a potent high of euphoria and relaxation would make it popular and extremely addictive among drug users¹³.

By the 1990s, U.S. law enforcement agencies began discovering clandestine laboratories producing illicit fentanyl and began to detect fentanyl in batches of heroin¹². Initially, fentanyl had been added to heroin mixtures to boost its potency, but fentanyl began to replace the popular heroin in the illicit drug market¹⁴. Heroin users who did not know of the fentanyl in their heroin were not used to the potent effects of fentanyl, hence leading to "an alarming increase in fentanyl-related deaths that were traced to fentanyl-laced heroin sold to unsuspecting heroin users" in the Midwest and Northeast regions from 2005 to 2006¹².

From the early 2000s to now, various statistics from the National Forensic Laboratory Information System support that fentanyl has become a greater issue. In 2015, fentanyl encounters climbed to 14,440 in the U.S., with every state reporting one except for South Dakota, and again most of these in the Midwest and Northeast¹². In addition, from 2013 to 2014, the number of fentanyl seizures increased by 259%¹². These trends only indicate a consistent increase in fentanyl use and dangerous health risks associated with addiction¹². From 2013 to 2016, "the number of fatal overdoses from synthetic opioids, primarily fentanyl and its analogs ... increased by 88% per year"¹¹. By 2017, deaths involving these synthetic opioids continued to increase while the incidence of heroin overdose deaths stabilized, implying that illicit fentanyl use is becoming the primary cause of the opioid crisis compared to other opioids that have previously seemed to be an issue¹¹.

In addition, the global scale of the current fentanyl crisis is largely underestimated and unprecedented due to the international network enabled by the Internet, specifically through the "dark web"¹². Encrypted sites using anonymization network tools allow drug users and dealers to form anonymous relations to expand counterfeit and illicit drug production and supply of these synthetic opioids¹². Therefore, through the influence of pharmaceutical companies and illicit drug manufacturers, increasingly more potent types of opioids pose a huge danger to the future of the U.S., especially in the regions where the drug market is already so integrated. Introducing dangerous alternatives that include mixing and lacing fentanyl into other drugs further emphasizes the need to act on the fentanyl crisis.

Fortunately, there exist safe drugs that can rapidly reverse the effects of an opioid overdose. These drugs act as opioid antagonists, which block the activation of opioid receptors from opioid molecules and hence treat opioid use disorder by preventing the opioids from producing addictive, rewarding euphoric effects¹⁵. Common medications are naltrexone and naloxone. Naloxone is often used for life-threatening opioid overdoses when there needs to be a quick reversal of the opioids' effects, as it can counteract the opioid drugs in the system¹⁶.

V. FENTANYL ANALOGS

Analogs have molecular structures similar to that of the drugs it mimics, hence being synthetic or designer drugs. As implied, fentanyl analogs are similar to fentanyl in chemical structure but can be more dangerous as they can be manufactured to be more potent and can not be routinely detected by drug tests. Due to the illegitimate production of these analogs, "hundreds of synthetic substances have been introduced to the illicit drug market over the last ten years," so much is still unknown about these emerging fentanyl analogs¹⁴.

Legitimate fentanyl analogs, such as sufentanil and alfentanil created by Janssen Pharmaceuticals in the 1970s, and remifentanil by Glaxo Wellcome in 1996, were created to be medical options as a potent analgesic that offered pain relief in a short duration of action, an adjunct to anesthesia¹⁴. By the 1990s, only occasional overdoses were reported, which were mainly due to medical misuse of potent systemic analogs accessed by medical professionals¹⁴. However, as new extremely potent analogs began being synthesized illicitly by groups of underground industrial chemists who supply and distribute

locally produced opioids, these deadly drugs began to be more widely accessible to the public as a product, hence increasing the number of overdose deaths from self-misuse¹⁴.

However, the recent barrage of different fentanyl analogs into the US drug market has demonstrated an international scale. Most of these analogs are manufactured in China, sold over the Internet, and enter the U.S. through Canada and Mexico¹². This contribution of the synthetic fentanyl analog epidemic adds to the opioid crisis and increasing number of deaths. It is necessary to prevent users from getting their hands on more potent and unfamiliar drugs that provide more lethal highs. In addition, as analogs are specifically designed, drug tests often can't pick up on them³. To prevent this rapid spread, forensic toxicology laboratories must find an effective routine drug screen to detect such synthetic compounds¹⁴.

VI. METHADONE

Methadone is another synthetic opioid, but more commonly used to treat opioid addiction and dependence. As a narcotic agonist that stimulates the same opioid receptors activated by other opioids, methadone has similar effects of being able to manage pain and being addictive¹⁵. However, being on methadone differs from the dangerous addiction to illicit opioids like heroin and fentanyl. Because methadone activates the receptors more slowly than other opioids, it can reduce cravings and eliminate withdrawal symptoms of stronger opioids, also reducing feelings of euphoria¹⁵. Therefore, people who are dependent on potent opioids like heroin, which have severe withdrawal symptoms and cravings, can replace using heroin with methadone to reduce harmful drug usage¹⁷. In addition, as it is taken orally, it eliminates the need for injecting drugs like heroin, which reduces the chances of HIV transmission¹⁷. Because of these properties, methadone helps gain abstinence from strong, harmful drugs to get users on the path to successful recovery from opioid use disorder through methadone maintenance treatment¹⁷.

VII. CASE STUDY: KENSINGTON, PHILADELPHIA

Kensington, a community in Philadelphia, Pennsylvania, has become infamous for being the epicenter of the opioid crisis in America. Ravaged by homelessness and crime, the Kensington streets are strewn with trash and bodies injected with drugs. Within the visible grime of the community are millions of dollars circulating due to the Kensington economy based on this drug trade, even called "the largest open-air narcotics market" with a supply of the cheapest and purest heroin on the East Coast¹⁸.

With this title, drug users and dealers from all over the region flock to get a hold of cheap heroin. However, due to the increase in users and want of higher doses, more opt for dope with more powerful effects: fentanyl, which is known to be a potent synthetic opioid that brings excruciating withdrawals and severe addiction. Now, with the unpredictable amounts of fentanyl, users in Philadelphia fall victim to the addiction induced by the powerful opioids. And since it is so accessible, users get their hands on more of it, leading to high overdose rates. In a 2018 report for Philadelphia, "deaths related to fentanyl had increased by 95 percent in the past year"¹⁸.

Of the ten most populous counties in the US, Philadelphia County has the highest overdose rate, and within the county, the Kensington neighborhood is "part of the largest cluster of overdose deaths"¹⁸. Even with increasing city-led initiatives, recovery centers, and projects to push toward economic mobility and improve the homelessness issue, the drug problem continued to persist in Kensington. Meanwhile, drug dealers began creating new and more potent drug combinations since fentanyl's high wasn't as long-lasting as heroin, so they wanted to "give it legs"¹⁹. A new issue has overtaken the Kensington community: xylazine.

Xylazine, often known as "tranq" on the streets, is an animal sedative approved for veterinary use. However, because it is used commonly in the veterinary industry, it is not controlled or limited, which makes it highly accessible and relatively inexpensive²⁰. This makes it more dangerous on the streets, as it has been increasingly used as a common additive to illicit drug mixtures composed of synthetic opioids, specifically fentanyl¹⁶. Apparently, adding xylazine to these illicit drugs provides benefits of enhancing drug effects and increasing the drugs' street value by increasing their weight¹⁶. However, as users are unaware of this, these drug mixtures increase the potential for fatal drug poisoning and overdoses, which is even underestimated because many aren't unaware of these drug combinations¹⁶.

As a sedative, xylazine can "substantially prolong a fentanyl high" and dangerously lower blood pressure, heart rate, and respiration²⁰. In addition, xylazine imposes great health issues, as drug users who repeatedly ingest substances containing xylazine have open wounds and sores, leaving black, dead tissue²⁰. Users lapse into blackouts, and the high wears off by the time they awake, so they become desperate for more doses²⁰. This dangerous process repeats, and unknowingly, the

user's skin rots, hence giving xylazine the name "zombie drug"²⁰. Tranq is being used in growing quantities and spreading into other sectors of the US outside of Philadelphia, such as Skid Row in Los Angeles, and the inability to even effectively identify xylazine's presence in cheap street drugs is creating greater issues²⁰. In addition, since xylazine is not an opioid itself, just frequently combined with them, its effects can not be reversed with medications like naloxone¹⁶.

This highlights the potency of street drugs and combinations of high doses of synthetic opioids which users unknowingly inject. There are so many victims just in this small community in Philadelphia that multiple organizations and city plans have failed to address, not to mention similar communities like Skid Row that reflect the homelessness and drug issues present in the U.S. But little by little, efforts are definitely being made. For example, Savage Sisters, a harm-reduction and recovery group for substance addicts, offers recovery housing and mental health programs to help those use substances for their problems to "numb their pain"¹⁹. As Sarah Laurel of the Savage Sisters says, "We need to address the pain; we need to stop isolating the substance and look beyond it"¹⁹.

VIII. GLOBAL INVOLVEMENTS

A. China

Historically, China has been long infected by the opioid epidemic since the initial spread of opium through Eurasia among the ancient civilizations through Arab traders⁵. Chinese civilians banned from smoking tobacco instead replaced it with opium, encouraging opioid use⁵. During the 1600s, large operations in India with the East India Company began mass distribution of opioids, which later was acquired by the British government⁵. Due to the skewed relations between the Western powers and China regarding trading, the British utilized China's opioid addiction problem to their advantage and encouraged the smuggling of drugs from India into China⁵. This caused significant financial and social issues in China, leading to the Opium Wars.

The opium problem still exists in China and has a significant grasp on opioid production internationally. Many of the synthetic precursors and illicit synthetic opioids, especially most of the fentanyl analogs, originate from China. Following the opioid crisis announced in 2017, the Trump Administration hailed an effective ban on fentanyl exports to the United States in 2019, which seemed to be the solution to the smuggling of illicit drugs from China²¹. However, Chinese chemical companies instead began to sell and ship precursor chemicals for producing fentanyl to drug cartels and black market dealers in Mexico²¹. Chinese and Mexican criminal groups have historically been seen to work closely for money laundering and regulating fentanyl and its precursor chemicals²². Despite legal actions made against China and its narcotics trade, the international black market makes it easy to smuggle into the United States, which could not counter the epidemic.

However, China largely denies its role in the fentanyl crisis, instead blaming it on America's social issues and the corrupt US pharmaceutical industry²¹. Although America's faulty health care system and industries are a huge factor in its spread, it is undeniable that China has the hold of most of today's fentanyl and synthetic opioid-related substances that are affecting American communities and the worldwide opioid crisis.

B. Canada

Canada's experiences with the opioid epidemic are quite similar to the problems faced in the U.S. as to the timing and severity of the crisis. This is partly due to Canada having a prior overdose crisis involving prescription opioids and many factors seen in the American epidemic also playing a role in Canada²³. In the 1980s, it was seen that "the volume of opioids sold to hospitals and pharmacies for prescriptions in Canada has increased by more than 3000%", making it "the second-largest consumer of prescription opioids in the world" after the U.S. by 2016²⁴. The prevalence of opioid misuse in Canada can especially be seen in the illicit use of prescription opioids as a survey from Health Canada revealed that a third of opioid users did not have a prescription in 2017²⁴. This illegal sharing and use of opioids for nonmedical purposes could be through routes like "double doctoring, prescription fraud and forgery, street drug markets, thefts, and Internet purchases," but the most common source was through family members²⁴.

There are socioeconomic factors that play in Canadian communities plagued by the epidemic as well. For example, impoverished neighborhoods in Canada that have limited access to healthcare and proper treatments have increased in overdose deaths and first-responder calls, in which "fentanyl was detected in 52% of the subjects who were prescribed opioid agonist therapy"¹¹. Since 2017, more opioid-related deaths have arisen, implying that the opioid crisis is also thriving in Canada, which fentanyl and analogs are fueling¹¹. In addition, Canada's existing medical policies differ from the United States, making it more susceptible to illicit smuggling. The high demand for diverted pharmaceuticals increased the smuggling of counterfeit pills from China into Canada, and hence easier for users in the U.S. to illegally access²³.

IX. CONCLUSION

Seen from just the statistics, opioid overdoses are increasingly claiming lives as it is being misused and abused throughout the years. We must consider that these statistics are considerably underestimated, as this is an international problem causing detrimental impacts on some of our American communities, specifically in the Midwest and Northeast regions where there is easy access to illicit drugs, especially due to advancements of technology and the dark web. As analyzed in this paper, synthetic opioids, specifically fentanyl and illegitimate fentanyl analogs, dominate this addiction crisis. These synthetic opioids, from both pharmaceutical influences and illegal factories, are purposely created to be more powerful and addictive to gain more profits. This greed and corruption have cost many lives led by the misuse and abuse of drugs.

However, there are ways to prevent our close ones from falling victim to this opioid crisis. Safe drugs such as naloxone and methadone can treat opioid overdoses, serving the purpose of what drugs were supposed to do: to help and treat. Advanced technology can detect dangerous drugs and prevent further spread. Still, the most important goal we must achieve is to become educated on the dangers of these synthetic opioids and such drugs in general. It is so easy to fall into the cycle of addiction as these synthetic drugs were designed to do so. In addition, our doctors who are responsible for identifying and treating our pain need to be able to prescribe opioid medication more carefully, as most overdoses happen because of initial over prescriptions. We must all be conscious of the effects of opioids and how overdoses happen to avoid dangerous situations and fend off the ongoing health crisis.

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