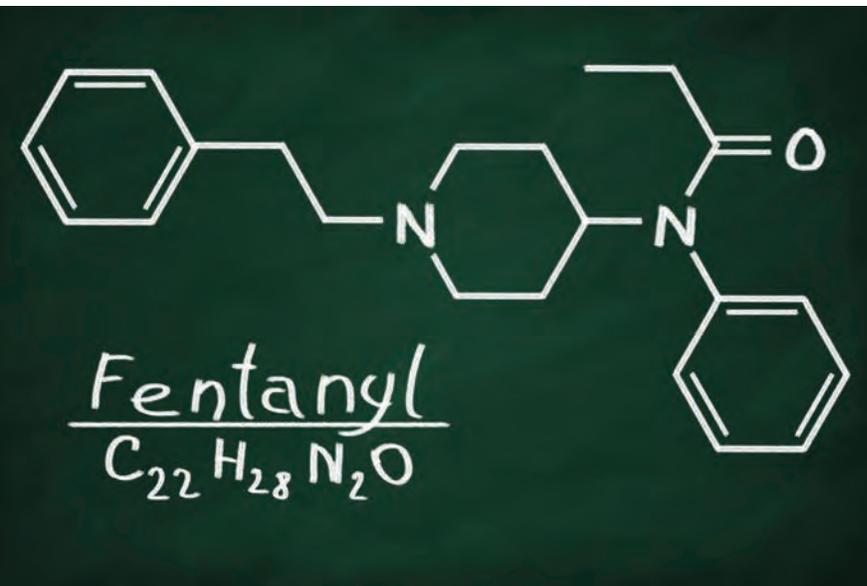


Fentanyl: The Third Wave of the Opioid Crisis

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You probably know the statistics: 91 people die every day in our country from an opioid overdose.¹ For several years, the opioid crisis has dominated the attention of NIDA and other federal agencies that address drug use and its consequences. It began in the late 1990s with the overprescribing of pain relievers like OxyContin, which led to escalating rates of opioid addiction and overdose deaths. An estimated 4–8 percent of people who misuse prescription opioids shift to heroin use within 3–5 years,^{2,3} as street opioids are considerably cheaper than their prescription relatives and produce essentially the same effects; this ultimately fueled the second wave of the opioid overdose epidemic. Federal agencies moved to address the crisis by recommending more limited use of prescription opioids by healthcare providers — which can help stem the tide of new opioid use disorders — as well as by recommending increased adoption of medication-assisted treatment and wider use of naloxone to reverse overdoses. But now our country is rapidly being caught up in what is being called a “third wave” of the opioid crisis: a surge in fatalities related to fentanyl, heroin’s much stronger cousin. This is presenting a host of new challenges.

Fentanyl, like heroin and prescription analgesics, is a mu-opioid receptor agonist, but it is considerably more potent than other opioids — 50–100 times more potent than morphine, for example. Adding to its dangers is its high fat solubility, allowing it to enter the central nervous system very rapidly. These properties dramatically increase the risk for addiction and overdose. Just 2 milligrams can be lethal,⁴ and even police officers and first responders are endangered by accidentally coming into physical contact with or inhaling fentanyl.

Fentanyl is not a new drug. It was first approved by the Food and Drug Administration in the 1960s, and more recently has been approved in various forms including a transdermal patch, a fast-acting lollipop, and a dissolving tablet and film. Because of its high potency, it is a medication mostly reserved for palliative care or surgical pain. Misuse of prescription fentanyl was described first in the 1970s and is still reported some people

who misuse prescription opioids.⁵ However, the bulk of the current fentanyl problem is not from misused or diverted prescriptions but from fentanyl illicitly manufactured in China and imported into the U.S., either directly via the mail or via Mexican drug cartels, who smuggle it across the border.⁶

The suddenness of this new threat is reflected both in seizures by law enforcement and in overdose statistics just over the last few years. The U.S. Drug Enforcement Administration (DEA) reported fewer than 1,000 fentanyl seizures in 2013, rising to 13,000 in 2015.⁷ Overdose deaths attributed to synthetic opioids tripled from 3,105 in 2013 to 9,580 in 2015¹; this category is dominated by fentanyl but also includes U-47700 (about 12 times more potent than morphine), acetyl-fentanyl (about 15 times more potent than morphine), butyrfentanyl (more than 30 times more potent than morphine), and carfentanil (used as a large-animal anesthetic in zoos and approximately 10,000 times more potent than morphine), among others. Numbers of known fentanyl deaths likely underestimate the problem, since one fifth of overdose death certificates do not list the specific drug involved,

and many medical examiners do not test for fentanyl.⁸ A NIDA-funded HotSpot study in New Hampshire, the state hardest hit by the fentanyl overdose crisis (in terms of overdoses per capita), found that nearly two thirds of the 439 drug deaths in that state in 2015 were caused by fentanyl.⁹

Fentanyl’s ease of manufacture from legally obtainable precursor chemicals and its high potency make it enormously profitable to manufacture and distribute, accounting for its rapid expansion in the illicit drug market. According to the DEA, a kilogram of fentanyl purchased in China for \$3,000 to \$5,000 can generate over \$1.5 million on the black market¹⁰ — much more than an equivalent amount of heroin, which is not only much less potent but is more expensive to produce as it must be extracted and processed from opium poppies. Because of its profitability, distributors are eager to put fentanyl in heroin or cocaine powder or in counterfeit prescription drugs. Fentanyl is often sold in capsules or pressed into pills made to look like prescription pain relievers or sedatives like Xanax.

Although many who overdose on fentanyl have taken the drug unwittingly, believing they are taking another drug, a surprising number of people are deliberately seeking it out. In most respects, the population of fentanyl users overlaps that of heroin users. Apart from questions of access and cost, people with opioid addiction may also be drawn to higher potency street products because of the opioid tolerance they have developed. This also appears to be driving some heroin users to deliberately seek out fentanyl. The NIDA-funded HotSpot study interviewed opioid users in New Hampshire and found that about a third knowingly sought fentanyl because of its reputed high potency: “Some may seek out a certain dealer or product when they hear about overdoses because they think that it must be good stuff.”⁹

What can be done? The challenges of a public-health and public-safety response to fentanyl are several. People are coming into contact with this drug via their addiction to other drugs. That drug is heroin in many cases, but many have also been hospitalized or killed when their cocaine was laced with fentanyl or when they have purchased tainted counterfeit pills. Thus

general drug prevention efforts are relevant, and the preventive measures being taken to quell the opioid crisis, such as stricter guidelines on opioid prescribing, can help prevent people from developing opioid addictions. To the same end, NIDA is actively funding research to find new treatments for pain. Recently two NIDA-funded research teams have reported success in preclinical research on opioid compounds that reduce pain in animals but are not reinforcing.¹¹ Other avenues such as targeting the endocannabinoid system instead of the opioid system are also being extensively studied, as are nonpharmacological approaches like transcranial magnetic stimulation. Hopefully in the next decade, physicians will have a wider array of tools to treat pain that do not pose the danger of dependence, addiction, and overdose that opioids do.

Since most fentanyl users are already addicted to heroin or other drugs, harm-reduction and addiction treatment are particularly important prongs in the public health and public safety response to the crisis. The opioid antagonist naloxone is a mainstay of harm-reduction efforts and its wider implementation, facilitated through easier-to-use nasal sprays, has saved many lives in the last few years. But fentanyl's extremely high potency often renders the usual doses of naloxone ineffective at reversing fentanyl overdose. Emergency departments are reporting increased numbers of cases in which multiple doses of naloxone are required, and there have been case reports of patients requiring intravenous administration.¹² Physicians and first responders need to be aware of this possibility and be prepared to administer naloxone in an appropriate dose and for an appropriate duration. The opioid education and naloxone distribution programs that have been so successful when implemented among opioid users remain crucial, but unless they are expanded to a broader group of drug users they will not help cocaine or sedative users who unknowingly ingest fentanyl or fentanyl-laced drugs; and given the potentially insufficient dose, lay-distributed naloxone may not be effective for opioid users who overdose on fentanyl. There is a clear need for research on overdose-reversal medications that would work better for fentanyl and other high-potency opioids.

An area where NIH-funded research has made some progress, crossing the domains of harm reduction and treatment, is in studying the possibility of vaccines against fentanyl and other opioids.¹³ Recruiting the body's own immune system to neutralize drugs in the bloodstream, via antibodies, before they enter the brain has been the subject of investigation for several years. Vaccines against opioids have been found to work in animals, but more research is needed to take these preclinical findings and develop them into products that can be tested in humans as tools to treat addiction or reduce its harms.

Lastly, expanding access to existing, effective addiction treatments, especially medications for opioid use disorders, is more important than ever. The sooner an opioid user receives buprenorphine or methadone to quell cravings and withdrawal symptoms, the greater the likelihood of averting the worst outcomes of his or her addiction, including overdose death from fentanyl-laced heroin or deliberate escalation from prescription opioids to even more dangerous, higher-potency substances. Unfortunately, fewer than half of private-sector treatment programs offer medications for opioid use disorder, and only a third of patients in those programs actually receive it.¹⁴

The fact that effective treatments for opioid use disorders exist but are so little utilized remains the clearest and theoretically most surmountable barrier in addressing this epidemic, which began with the overprescription of pain medications nearly two decades ago. The dire risk of overdose death in the current environment should overwhelm any lingering attitudinal resistance against such treatments held among treatment providers, since an opioid user who dies of an overdose stands no chance of recovery. And

the flood of overdose victims into emergency rooms provides real economic incentive, on top of the moral imperative, for healthcare systems to make sure these effective and cost-effective measures are widely utilized. The fentanyl "third wave" is yet another wakeup call that we must do more to deliver effective addiction treatment to people who need it.



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