

Fentanyl Analogues

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Fentanyl was first synthesized by Paul Janssen in 1959 (Janssen, 1965) and was derived from the synthetic opioid, meperidine. Its pharmacological action is 50–100 times more potent than morphine, 25–40 times more potent than heroin, and it is commonly used in anesthesia and pain treatment (US Drug Enforcement Administration [US DEA], 2015; National Institute on Drug Abuse [NIDA], 2016). Fentanyl and its clinically used analogues are regarded as highly potent mu (μ) opioid receptor agonists. The μ receptor is responsible for dopamine release, which results in euphoria, and control of the breathing mechanism. The μ activity, along with the kappa (κ) and delta (δ) activity, is a characteristic of the opioids.

Fentanyl, which has meperidine (Demerol) as its synthetic building block, shares chemical structural characteristics of all the fentanyl analogues. There are 20 to 30 of these compounds that have opioid properties. Some of the more well-known fentanyl analogues are carfentanil, acetyl fentanyl and Cis-3-methyl-fentanyl, just to name a few. When compared to the activity of morphine, some of these analogues have very strong binding and activity at the μ receptor, however, a great number have weaker binding and less activity. The real danger of fentanyl and its analogues is with those that have stronger binding and greater activity compared to morphine. These compounds, when added to morphine, heroin, or other illicitly made substances and then sold on the street, are the ones that are responsible for the spike in opioid overdose and

death. The unsuspecting user assumes that the composition and strength of the substance that they are self-administering is that of morphine. In 2016, fentanyl and its analogues were the most common cause of overdose deaths in the United States at more than 20,000, which was about half of all opioid-related deaths. Most of these overdose deaths were due to illegally made fentanyl. First responders and emergency rooms are equipped with naloxone to combat cases of breathing cessation. When administered, naloxone replaces the fentanyl on the μ receptor and breathing is restored. Monitoring and multiple doses of naloxone are necessary during elimination of the fentanyl to safely restore normal breathing of the patient.

In 2013 the actual appearance of fentanyl and fentanyl analogues in deaths appeared sporadically across the United States. In 2014 illicit pills containing fentanyl, fentanyl analogues, and other novel synthetic opioids such as U-47700 began to appear. Fentanyl analogues were detected in drug related deaths as well as in confiscated materials and pills found at the scene of the death. Fentanyl and its manufactured analogues have completely infiltrated North America and have caused deaths in every state. The compounds have been mixed with heroin, morphine, synthetic opiates, cocaine, and methamphetamine. These compounds are relatively cheap to produce and are very powerful, which makes the addition of a small amount appear more effective when mixed with the other drugs. The evolution of fentanyl and development of the many analogues with varying strength, combined with the lack of knowledge of the potency and danger of

these drugs, have led to the “opioid epidemic” that we currently have today.

On the positive side, fentanyl is extensively used in the hospital environment with good results. When administered by professionals it is very safe, potent and extremely useful as a pain reliever and sedation inducer. It is excellent for acute onset of pain and for the treatment of long-term pain in cancer patients. The dose required is substantially less than a therapeutic equivalent dose of morphine, and extremely fast acting for relief of acute pain onset.

Opioid treatment clinics have a dilemma; there are limited options for rapid detection for fentanyl, which makes laboratory testing essential to determine what substances patients are taking. A positive result through immunoassay testing should be confirmed to determine the analyte that is present, or if there was a possible cross reaction with another substance. Of the 20-30 fentanyl analogues, it would seem a relatively small number of fentanyl analogues are typically mixed into other illicit substances before being sold. It will take some time and more research before fentanyl and its cross reactions are fully understood.

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