

The Emergence of Fentanyl and Fentanyl Analogues as a True National Security Threat

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January 2019 – Unpublished

Introduction

On April 26, 2018, Nebraska Highway Patrol pulled over a tractor trailer with U.S. Mail markings that was swerving across the road on Interstate 80 near Kearney, NE (130 miles west of Lincoln). [1]. As they searched the truck, they discovered a secret compartment containing what was eventually confirmed to be 118 pounds of the drug fentanyl—an amount that could provide a lethal dose to more than 26 million people [2]. Fentanyl is a powerful painkiller that is approved by the Food and Drug Administration (FDA) for legal use under certain circumstances, but increasingly is being used for recreational use, and has been a key contributor to overdoses and deaths associated with the opioid epidemic [3]. Moreover, fentanyl (and its analogues) has been studied for use as an incapacitating agent [4,5], and there are concerns that it could be weaponized and employed in this capacity on the United States homeland or against U.S. forces abroad. Aside from obvious concern in the homeland security, law enforcement, and public health communities, recent projects supported by U.S. Army Research, Development & Engineering Command Edgewood Chemical Biological Center (RDECOM ECBC) and U.S. Army Medical Research Institute for Chemical Defense (MRICD) further highlight interest in this issue by the U.S. Department of Defense (DoD) [6-9].

The increasing amount of fentanyl, fentanyl analogues, and counterfeit fentanyl-related drugs entering the country is sounding the alarm among the public health and homeland security policy communities. Shipments coming to the U.S. from China and Mexico, such as the truck discovered in Nebraska, are growing in frequency. In fact, fentanyl seizures by U.S. Customs and Border Patrol (CBP) along the U.S.–Mexico border increased by 135 percent between 2016 and 2017 [10]. Additionally, the U.S. mail service and other legitimate carriers are being used unwittingly to transfer counterfeit fentanyl into the country, primarily from China [11]. The dire health effects of fentanyl are taking their toll on first responders, especially law enforcement and working canines [12]. Its ease of production, illicit sales, and increase in trafficking makes fentanyl and its analogues easier to obtain, thus more likely that they could be used in an attack. These challenges, among others, are prompting action from federal, state, and local authorities to mitigate health and security concerns related to this threat.

All About Fentanyl

Fentanyl is listed as a Schedule II drug under the Controlled Substances Act of 1970 [3]. First discovered in 1959, fentanyl was first put into use almost immediately as an anesthetic [3]. Fentanyl is a μ -opioid agonist that rapidly crosses the blood-brain barrier, causing potent effects in the central nervous system [13]. Effects of fentanyl include euphoria, sedation, confusion, pain relief, and respiratory depression [3]. It is these effects that make fentanyl an efficient anesthetic and pain killer, as well as what makes it a dangerous but effective incapacitating agent. As little as two milligrams of fentanyl—about the size of a few grains of table salt—can be fatal to humans [14]. Due to its unique chemical structure, simple changes to various aspects of the molecule can continuously yield an almost unlimited number of combinations [15]. Each of these structures using the core fentanyl molecule belong to a family known as the fentanyl series, fentanyls, fentanyl analogues, fentanyl-related compounds, or fentanyl-related substances (FRS) [10,15]. Altering the core molecule does not change the mechanism of action but does alter the potency. For example, certain less commonly used analogues are 110-450 times less potent than fentanyl [15], but another analogue, carfentanil, is 100 times more powerful than fentanyl. Its only intended use is as a

tranquilizer for large animals [16]. Carfentanil has already been deployed as an incapacitating agent, according to information collected during the 2002 Moscow Theatre Hostage Crisis (see more below) [17].

Challenges of Fentanyl

Fentanyl is extremely effective as an analgesic when used as prescribed under highly controlled circumstances. However, fentanyl and its analogues are extremely dangerous when used improperly. Accordingly, they present a substantial threat to public health and safety. The emergence of non-pharmaceutical uses of fentanyl and its analogues can be placed into three categories, each of which is briefly explained below.

Illicit Trafficking

Compared to other drugs and narcotics, fentanyl is fairly easy to manufacture. It requires fewer precursor materials and minimal production facilities. Fentanyl is also cheaper to manufacture than other drugs [10,14]. Because of these traits, fentanyl plays a major role in the economics of transnational crime organizations and drug cartels. Illicit fentanyl enters the U.S. in one of two ways. First, the production of fentanyl (and its precursors) is not regulated in China, and until May 2018, carfentanil was available for online purchase. It has been extremely easy to purchase fentanyl through the darknet, using a cryptocurrency to remain anonymous and utilizing the U.S. mail service and other shipping companies to deliver it directly to a consumer's doorstep [18]. Additionally, counterfeit fentanyl is commonly made in China and sent overseas. Fake fentanyl easily enters both the legal and illegal supply. Chinese-manufactured fentanyl can also be shipped to Mexico or Canada and then transported to the U.S. [10].

Fentanyl is also produced in Mexico and shipped to the U.S., where its sale helps fund drug cartel activities. Due to its low manufacturing cost, fentanyl is being used to stretch the supplies of other illicit drugs (including heroin, and to a lesser extent, cocaine) [19]. These drugs are cut with fentanyl and sold for less, but also allow heroin supplies to last longer, leaving the cartels with more money. Unfortunately, fentanyl-contaminated heroin is extremely deadly and has caused an increase in the number of overdoses and deaths attributed to the current opioid health crises. The influx of fentanyl across U.S. borders makes it readily available for other nefarious uses. Notably, the rise in illicit fentanyl trafficking has been identified as a National Security Issue outlined in the *National Security Strategy of the United States of America* [20].

Use as an Incapacitating or Calmative agent

In October 2002, Chechen terrorists attacked a Moscow theater and took approximately 800 hostages [5,17]. After a three-day standoff in which multiple hostages were killed, the Russian Federal Security Service (FSB) authorized a Special Forces unit to end the siege. An unidentified gas was pumped into the theater, immobilizing the terrorists. Unfortunately, more than 100 people died (including nearly 20 percent of the hostages), primarily due to the effects of the gas. While the move was largely praised among the international law enforcement community—as it arguably prevented most or all of the hostages from dying—the Russian government faced pressure to release the identity of the incapacitating agent used at the theater, later revealed to be a compound of fentanyl derivatives named Kolokol-1. Test of the victims' clothes then confirmed that the agent most likely contained an aerosolized remifentanil-carfentanil mixture [17].

An incapacitating or calmiative agent is one that acts on “higher regulatory activity of the central nervous system [and] produce[s] a disabling condition,” typically disorientation, sedation, or unconsciousness, as witnessed in the Moscow theater crisis [21]. An effective incapacitating agent generally has the following characteristics:

- High potency
- Rapid onset
- Short, defined duration
- Reversible effects
- Stability in storage/transit
- Predictable effects at given doses
- Rapid dissemination in controllable amounts
- High safety margin [4]

For the most part, fentanyl and its derivatives possess all of these characteristics; thus the interest from many countries, including the United States, to develop incapacitating agents based on fentanyl [21,22]. However, it is the lattermost characteristic—high safety margin—that makes fentanyl and its derivatives attractive incapacitating agents. For example, in August, 2018, Nebraska became the first state in the U.S. to use fentanyl in an execution [23].

Safety margin, or therapeutic index, is the gap between an effective sedative dose and a lethal dose. This gap is smaller with fentanyl (and certainly smaller still with many fentanyl derivatives) than other commercially-available analgesics and sedatives. For example, carfentanil causes severe respiratory depression and death in nonhumans at doses ranging from 2–14 µg/kg, just 7–50 times the effective dose for analgesia [4]. A 2018 report from MRICD was the first to report “real-time respiratory dynamics and cardiac function” following exposure to aerosolized carfentanil [7].

First Responder and Canine Exposure

The increasing amount of fentanyl trafficked into the U.S. has posed not only a public health problem for opioid users, but also for first responders (e.g., law enforcement, firefighters, emergency medical services, and military), as they are increasingly coming into contact with fentanyl and fentanyl-contaminated heroin and -cocaine during investigations and routine stops. In fact, there have been several instances of first responders requiring medical treatment and hospitalization following exposure to known or suspected fentanyl or carfentanil powder [24]. Even worse, working canines can be and are exposed to fentanyls during the course of their mission, and unfortunately can be exposed to lethal doses quite easily [25]. The situation has grown so serious that multiple organizations and agencies, including the White House and the National Institute for Occupational Safety and Health, have issued special guidance to first responders regarding how to handle fentanyls or suspected fentanyls in the field [26,27]. Potential exposure to weaponized fentanyl is also a concern, and much of the issued guidance pertains to intentional use of fentanyl. In early 2018, members of the South Carolina Army National Guard received specialized training related to the safe handling of fentanyl and its precursor materials [28]. The threat landscape is changing so rapidly that non-traditional entities are in danger of being exposed to fentanyls through routine acts and terror situations alike.

Mitigation Efforts

Although initially well-received, the 2002 Moscow crisis eventually came to raise alarms within the national security community, due to how successful and effective Kolokol-1 was. Since then, many efforts in the U.S. have focused on more safely

identifying substances that could contain fentanyl and countering its effects. Aerosolized fentanyl is a highly effective incapacitating agent, and aerosolized sufentanil and carfentanil may be at least as toxic as the nerve agent VX [4]. MRICD recently estimated that the median lethal dose of carfentanil (in ferrets) is 27.77 µg/kg, demonstrating why the interest as a potential terror agent [6]. Current efforts focus on two major aspects of technology development to mitigate exposures of the fentanyl series: chemical detection, and medical countermeasures. Funding for these initiatives seems to be mixed with most sensor and detection technologies being funded by the Defense, Intelligence, and Homeland Defense and Security communities, whereas medical countermeasures are primarily funded by agencies of the U.S. Department of Health and Human Services. Prudence would suggest that these communities should share resources and discoveries to maximize the return on the government’s human and financial assets.

Sensors

One of the fastest developing areas of research and development in mitigating fentanyl involves sensors. These come in two forms: sensors developed specifically to identify fentanyls, and general-purpose sensors capable of identifying a wide range of chemicals, including fentanyls. In May 2018, the Department of Homeland Security awarded, through the Small Business Innovation Research program, research contracts to three companies (Nano Terra, Inc.; Polestar Technologies; and Vaporsens) to develop a wearable fentanyl analogue sensor that would “signal the presence of fentanyl and its analogues within minutes of contact” [29]. In contrast to a sensor worn by individuals, university research funded by the Defense Threat Reduction Agency (DTRA) supports the development of a synthetic protein that binds to fentanyl and acts as a sensor [30]. This complex can be placed inside plant cells and eventually into entire plants, which can be used as a warning system to alert military or law enforcement of the presence of fentanyl long before humans are sent to that area.

Looking at chemical sensors more generally, the Defense Advanced Research Projects Agency (DARPA) has launched programs that aim to develop sensors that can provide early detection of threats. The advanced Plant Technologies program aims to turn plants into “the next generation of intelligence gatherers” using advanced molecular and biotechnology technologies [31]. The Sigma+ program, which builds on the initial success of Sigma (a program dedicated to developing a network of radiation detection sensors), is expanding to include a chemical and biological detection network that could provide coverage for a large metropolitan area [32]. Looking forward, researchers at the Georgia Institute of Technology have developed a sensor that can identify chemicals while underwater, using a special attachment that mimics the mechanism of the star-nosed mole [33]. This device could be used to identify a threat, such as contamination of drinking water using fentanyls.

Chemical Identification

A major challenge in dealing with fentanyl and its analogues is the ability to detect their presence without putting humans or canines at risk. Most analytical methods require a sample be collected and analyzed in a machine, which requires a person to be in close contact with the substance. For example, TD-DART-MS and Ion Mobility Spectrometry are two of the most promising rapid detection methods under development, and while they have improved analysis time and sensitivity, they still require that an individual swab a surface [34,35]. Alternatively, point-of-contact testing allows first responders and others to use hand-held devices (e.g., TruNarc and Gemini)

to identify fentanyl. However, these devices can only detect concentrations of fentanyl greater than 10 percent [35]. Additionally, a new challenge is emerging in regard to the limitations for detecting the ever-growing number of fentanyl analogues [36]. RDECOM-ECBC, with funding from DHS, evaluated three commercial off-the-shelf hand-held devices and found that Express Diagnostics Int'l has developed a device that more accurately identified multiple fentanyl analogues in both urine and saliva samples [9].

The National Institute of Standards and Technology (NIST) is supporting the development of a hand-held device that could offer one solution to these challenges. NIST is working with DARPA to identify technologies capable of detecting a wide range of fentanyl analogues and be able to identify concentrations as small as 0.1 percent by weight [37]. One of the most ambitious projects is the Standoff Illuminator for Measuring Absorbance and Reflectance Infrared Light Signatures program, or SILMARILS, which is funded by the Intelligence Advanced Research Projects Activity. SILMARILS seeks to develop a portable standoff chemical detection system that can be sensitive at ranges of 30 meters and used for a variety of threats, including narcotics [38]. The ideal system will use active infrared spectroscopy and can be applied in multiple situations.

Vaccines

Vaccination is a term typically associated with infectious diseases (e.g., influenza), but more properly, a vaccine is anything that helps promote an immune response in the body to help it better fight off an external threat. With that concept in mind, interest has grown recently in the possibility of developing a vaccine that could help improve the body's defense against opioid exposure. Research is supporting vaccine development that could effectively combat the likelihood of experiencing an overdose after contact with fentanyl [39-41]. A broader vaccine for all opioids is also under development, but research suggests that vaccines may need to be developed for each class of opioids, given that Raleigh and colleagues determined in 2012 that an effective vaccine for heroin did not produce antibodies following fentanyl exposure [42].

Antidotes

As mentioned above, one of the desired characteristics of an incapacitating agent is that its effects be reversible. Fortunately, most opiate analgesics respond well to a medication called naloxone, which is a competitive mu opioid-receptor antagonist [43]. Naloxone can be administered via multiple routes, has minimal side effects, and can be given when body weight is unknown. For many years, naloxone was administered solely in a hospital setting, but the opioid health emergency has caused governments and regulatory agencies to re-think that decision,

and now naloxone is readily available for use by first responders and is even available for purchase over the counter in some places worldwide [44]. A startup in Vancouver, B.C., is developing a wearable device that would monitor the heart rates of narcotics abusers and could eventually be used for first responders or military personnel [45,46]. The ODETECT technology would detect when a pulse is no longer present and administer a dose of naloxone and alert first responders to the person's location [<https://www.brave.coop/products>].

One drawback to naloxone is that multiple doses may be needed to completely reverse the effects of a fentanyl dose. This is not an insurmountable problem when only one overdose victim is being treated; however, if multiple victims of fentanyl overdose are being treated at a time, naloxone may not prove to be a practical solution.

In response to concerns of how to manage an attack involving weaponized fentanyl, the Biomedical Advanced Research and Development Authority—part of the U.S. Department of Health and Human Services—recently awarded a California company, Opiant, a one-year contract to reformulate an existing opiate antidote [47]. Nalmefene was originally approved by the FDA in 1999, but was pulled from the market due to low sales. The new formulation would make the drug available in an intranasal form, which would be easier to administer in a mass casualty scenario, and nalmefene has been shown to be more effective than naloxone at reversing the effects of certain fentanyl derivatives, particularly carfentanil, sufentanil, and acrylfentanyl [48]. However, RDECOM-ECBC has demonstrated that naloxone, contrary to unsubstantiated reports, is effective at reversing the effects of acrylfentanyl [8].

Conclusion

Fentanyl is a powerful and effective tool in managing pain. Unfortunately, it is also a powerful incapacitating agent, potential weapon of mass destruction, and national security threat. The increase of illicit trafficking from Mexico and China has created a new danger to both public health and national security. It has already been shown that fentanyl analogues have the ability to easily render crowds unconscious, and this new reality requires new tools to counter the threat. In addition, the ever-increasing amount of fentanyl analogues entering the illicit market has added a new challenge in developing equipment sophisticated enough to identify suspected but unknown, emerging threats. Technologies supported by DoD and other agencies are improving the capacity of law enforcement, border patrol, and military forces to mitigate nefarious uses of fentanyls; however, it will take time and cooperation to rise to the level of security needed to protect the U.S. and its citizens posed by this this novel and sobering challenge.

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