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Rising Numbers of Deaths Involving Fentanyl and Fentanyl Analogs, Including Carfentanil, and Increased Usage and Mixing with Non-opioids

Summary

This Health Alert Network (HAN) Update is to alert public health departments, health care professionals, first responders, and medical examiners and coroners to important new developments in the evolving opioid overdose epidemic, which increasingly involves illicitly manufactured fentanyl and an array of potent fentanyl analogs (i.e., compounds that are chemically related to fentanyl). It is the second update to the original health advisory, [HAN 384](#), issued October 26, 2015, which alerted the public to the increase in unintentional overdose fatalities involving fentanyl in multiple states, primarily driven by illicitly manufactured fentanyl. The first update to this health advisory was released on August 25, 2016 ([HAN 395](#)), describing the sharp increase in the availability of counterfeit pills containing varying amounts of fentanyl and fentanyl analogs, the continued increase of overdose deaths involving fentanyl across a growing number of states, and the widening array of fentanyl analogs being mixed with heroin or sold as heroin.

The current update includes information on: (1) the continued increase in the supply of fentanyl and fentanyl analogs detected by law enforcement; (2) the sharp rise in overdose deaths involving fentanyl and fentanyl analogs in a growing number of states, in particular the growing number of deaths involving the ultra-high potency fentanyl analog known as carfentanil; (3) the expanding number of poly-drug combinations implicated in opioid overdose deaths, which include non-opioids, such as cocaine; (4) the updated comprehensive guidance available to law enforcement and other emergency responders to prevent occupational exposure to fentanyl and fentanyl analogs; and (5) updated recommendations for public health professionals and health care providers regarding prevention and response efforts.

Background

The supply, distribution, and potency of illicitly manufactured fentanyl and fentanyl analogs in the U.S. drug market is continuously evolving. The Drug Enforcement Administration's (DEA) National Forensic Laboratory Information System (NFLIS), which systematically collects drug identification results from drug cases submitted for analysis to forensic laboratories (referred to as drug submissions), estimated that drug submissions testing positive for fentanyl more than doubled from 2015 to 2016, rising from 14,440 to 34,119. This increase continued into 2017, with an estimated 25,460 reports in the first six months of 2017 alone [1,2,3]. In 2016, states reporting the highest number of fentanyl drug submissions remained concentrated in the East and Midwest, with all being located east of the Mississippi River, or bordering the Mississippi River. This geographic clustering of states is believed to be related to the supply chains of the white powder heroin market, which predominates east of the Mississippi [10]. Illicitly manufactured fentanyl powder can be readily mixed with white powder heroin or mimic this form of heroin, while black tar heroin, which is primarily sold west of the Mississippi, is more difficult to blend with fentanyl powder.

During January–June, 2017, NFLIS received an increased number of reports from state and local forensic laboratories of fentanyl analogs and other synthetic illicit opioids (e.g., U-47700, described below) detected among drug submissions. This included two extremely potent fentanyl analogs, carfentanil and 3-methylfentanyl, which are 100 and 4 times more potent than fentanyl, respectively [4]. Carfentanil drug submissions reported to NFLIS rapidly increased from an estimated 1,251 in 2016 to 2,268 during the first six months of 2017 (see table below) [2, 3]. In 2016, a total of 11 states reported carfentanil drug submissions, including Ohio with more than 900 reports and Florida with more than 100 reports. The other 9 states each submitted between 1 and 49 carfentanil reports [3]. Further spread is expected as

new states report overdose deaths related to carfentanil in 2017. Other fentanyl analogs rising in prominence during 2016-17 are 3-methylfentanyl, furanylfentanyl, and acrylfentanyl (see table below) [2, 3]. Finally, drug submissions testing positive for a synthetic illicit opioid known as U-47700, first encountered by the DEA in 2016, increased from 533 submissions in 2016 to 1,087 during January–June, 2017 [1,2]. This newly emerging illicit opioid was temporarily placed under Schedule I control under the Controlled Substances Act in October 2016, allowing for criminal prosecution of those who possess, import, distribute, or manufacture it.

Number of drug submissions testing positive for fentanyl analogs and U-47700 in NFLIS in 2016 and during January–June 2017.

Fentanyl analog/synthetic opioid	2016*	January–June 2017^
Carfentanil	1,251	2,268
Furanylfentanyl	2,273	3,322
3-methylfentanyl	427	432
Acrylfentanyl	26	1,508
U-47700	533	1,087

*NFLIS Brief: Fentanyl and Fentanyl-Related Substances Reported in NFLIS, 2015–2016 & NFLIS 2016 Annual Report for U-47700.
 ^NFLIS 2017 Midyear Report. These data are preliminary, and may change in the Annual Report for 2017.

The dramatic rise in the supply of illicitly manufactured fentanyl and fentanyl analogs has been mirrored by an equally dramatic rise in deaths involving synthetic opioids other than methadone, a category which includes fentanyl and fentanyl analogs. The rate of synthetic opioid overdose deaths in the U.S. rose from 3.1 to 6.2 deaths per 100,000 between 2015 and 2016, marking the first year that synthetic opioids became the most common type of opioid involved in all opioid overdose deaths [5]. This trend has extended into 2017, with preliminary counts from the National Center for Health Statistics (NCHS) indicating that more than 55% of opioid overdose deaths occurring nationally in the 12-months ending November 2017 involved synthetic opioids, accounting for more than 27,000 overdose deaths [6]. This 12-month sum of synthetic opioid overdose deaths exceeds the total number of all opioid overdose deaths in 2013, when deaths involving synthetic opioids first began to climb.

Enhanced surveillance of opioid overdose deaths has been initiated in a growing number of states under a system that CDC funds known as the State Unintentional Drug Overdose Reporting System (SUDORS). This surveillance system is capable of identifying the specific fentanyl compounds involved in opioid overdose deaths [7]. In the 10 states (KY, ME, MA, NH, NM, OH, OK, RI, WV, and WI) reporting preliminary data for the period July 2016–June 2017, 7 states reported that 50% or more of all opioid overdose deaths tested positive for fentanyl, and 5 of the 10 states reported that 10% or more opioid overdose deaths tested positive for fentanyl analogs. The number of opioid overdose deaths testing positive for fentanyl or fentanyl analogs in these 10 states substantially increased from the second half of 2016 to the first half of 2017, with total fentanyl involved deaths rising from 2,986 to 3,303, and fentanyl analog involved deaths rising from 764 to 1,511. Notably, carfentanil deaths nearly doubled from 421 in the last half of 2016 to 815 in the first half of 2017, and became the most commonly detected fentanyl analog overall during this period in the 10 states reporting (1,236 deaths, 11% of all opioid deaths).

The next most commonly detected fentanyl analogs during July 2016–June 2017 in the 10 states were furanylfentanyl (518 deaths, 5% of all opioid deaths), acrylfentanyl (334 deaths, 3% of all opioid deaths), and acetylfentanyl (319 deaths, 3% of all opioid deaths). Ohio alone reported more than 1,700 opioid overdose deaths testing positive for fentanyl analogs during July 2016–June 2017, with more than 1,100 of those deaths involving carfentanil. This represents around 90% of all carfentanil deaths reported in SUDORS during this time period. Florida has also been highly impacted by fentanyl analog overdose deaths, and in particular by carfentanil. Although not funded to report data into SUDORS for the period July 2016–June 2017, Florida independently reported 1,274 fentanyl analog deaths in 2016, with carfentanil being the most commonly detected, involved in 43% of all fentanyl analog deaths (n=552) [8]. Florida and Ohio are also notable for having reported a widening array of fentanyl analogs among their opioid overdose deaths, with Florida detecting 8 different fentanyl analogs in 2016, and Montgomery

County, Ohio, detecting 8 different fentanyl analogs and other illicit synthetic opioids in the first two months of 2017 alone [8,9]. Finally, U-47700 was detected in 123 opioid overdose deaths in SUDORS and was widespread across the 10 states reporting, with at least one U-47700 attributable death occurring in 9 of these states.

Recent data from public health and law enforcement has revealed that fentanyl and its analogs are increasingly becoming available on the illicit market mixed with non-opioid drugs, particularly cocaine. In 2016, fentanyl compounds were detected in combination with other non-opioid substances in more than 1,500 drug submissions tested nationally by NFLIS, with over 60% of these involving a combination of fentanyl and cocaine [10]. The DEA released a bulletin in 2017 warning of the widespread adulteration of cocaine with fentanyl and fentanyl analogs in the state of Florida [11], as well as a January 2018 bulletin warning of the rising number of cocaine and fentanyl submissions in Pennsylvania [12]. During the period from 2016 to 2017, 180 cocaine drug submissions tested positive for fentanyl or fentanyl analogs in Florida, including acetyl fentanyl, carfentanil, furanylfentanyl, and p-fluoroisobutyryl fentanyl. In Pennsylvania, cocaine/fentanyl combination drug submissions rose 112% from 2016 to 2017, rising from 63 to 134 drug submissions during that period. In early 2017, health officials in New Haven, Connecticut, reported an outbreak of fentanyl overdoses among a group of opioid-naïve patients (no reported prior use of opioids) who had reported only the use of cocaine prior to being seen in the emergency department (ED) [13]. Three of these cases were fatal, with opioid-naïve persons being particularly vulnerable to the effects of an opioid overdose. Later that year, New York City (NYC) released a health advisory that included a warning to NYC residents that fentanyl was increasingly being detected among persons who overdosed on cocaine in 2016 [14]. It was further noted that The New York Police Department forensic laboratory had identified the presence of fentanyl in benzodiazepines, counterfeit opioid pills, ketamine, and methamphetamine. The DEA has reported limited but rising numbers of seizures of methamphetamine mixed with fentanyl and fentanyl-related compounds, with a total of 23 submissions across 10 states during 2014-2016 [10].

In response to these ongoing threats, CDC will begin providing at least yearly updates on the number of fatal opioid overdoses involving fentanyl and fentanyl analogs starting in 2018 from states participating in SUDORS. SUDORS expanded to 32 states and Washington D.C., in 2017, and is expected to expand further in 2019.

Recommendations

CDC suggests the following actions in response to the increased risk of fentanyl overdose from illicitly manufactured fentanyl due to the widening array of highly toxic fentanyl analogs and the combination of these fentanyl analogs with other non-opioid drugs, including cocaine and benzodiazepines:

(1) Improve detection of fentanyl outbreaks to facilitate effective response

- *Public health departments:*
 - Explore methods for rapidly identifying drug overdose outbreaks through use of existing surveillance systems such as medical examiner data, emergency medical services data, near-real time emergency department data, and poison center data [15].
 - Consider engaging local poison centers to assist with treatment of patients (national toll free phone number is 800-222-1222).
 - Track and monitor geographic trends in the illicit opioid drug supply, including the drugs with which opioids are mixed, using DEA's National Forensic Laboratory Information System (NFLIS) and National Heroin Threat Assessment Summaries and alerts on the DEA website [16] to inform prevention and response efforts.
 - Explore other methods for obtaining information on local drug supply, including building partnerships with local laboratories and High Intensity Drug Trafficking Area (HIDTA) units in order to receive data in a timelier manner.
 - Track decedent demographics and known risk factors for overdose (e.g., drug type, recent release from an institution, previous overdose) to inform prevention efforts [17].

- Raise awareness among key partners and stakeholders to the widening profile of those at risk for fentanyl overdose, which increasingly includes persons misusing diverted prescribed oral pain and sedative medications [21] and people using cocaine in some states [13,14].
- Develop general public health messaging about fentanyl, including fentanyl-laced counterfeit pills and fentanyl analogs that emphasizes the toxicity and potential lethality of the drug versus its high “potency.” The messaging should include warnings of the highly variable content of fentanyl present in illicit products, which further elevates risk of overdose, as well as the potential presence of fentanyl in cocaine [10,11,12,13,14,18]. For further guidance, see information about fentanyl on the CDC website (<https://www.cdc.gov/drugoverdose/opioids/fentanyl.html>)
- *Medical examiners and coroners:*
 - Screen for fentanyl in suspected opioid overdose cases in regions reporting high levels or sharp increases in fentanyl seizures, fentanyl-related overdose fatalities, or unusually high spikes in heroin or cocaine overdoses with signs of opioid toxidrome, or unspecified drug overdose fatalities.
 - Screen specimens using an enzyme-linked immunosorbent assay (ELISA) test that can detect fentanyl. Confirmatory gas chromatography mass spectrometry (GC-MS) of positive screens for fentanyl may either confirm the presence of fentanyl or suggest the presence of a fentanyl analog. [20]. When fentanyl screening is negative, or confirmatory testing is inconclusive, yet opioid or fentanyl overdose is highly suspected, consider specialized testing for fentanyl analogs, particularly if an increase in overdoses is occurring or fentanyl analogs have been detected in local drug products.
- *Law enforcement:*
 - Use extreme caution when handling suspected illicitly manufactured fentanyl, white powders, and unknown substances. For further guidance, see newly available CDC recommendations for protecting workers at risk (<https://www.cdc.gov/niosh/topics/fentanyl/risk.html>), as well as “Fentanyl Safety Recommendations for First Responders”, provided by the White House National Security Council (<https://www.whitehouse.gov/ondcp/key-issues/fentanyl>)
 - Prioritize and expedite laboratory testing of drug samples taken from drug overdose scenes, if possible.
 - Share data on fentanyl and fentanyl analog drug seizures with local health departments, medical examiners, and coroners.
 - Carry a supply of naloxone so that it can be administered immediately to mitigate the effects of an overdose. (See Recommendation 2 below.)
- *Laboratories:*
 - Utilize the following government forensic laboratories supporting law enforcement for assistance with reference materials or reference data on a case-by-case basis:
 - DEA Reference Materials Program (email: DEALabRefMaterials@usdoj.gov)
 - DEA Emerging Trends Program (email: DEA.Emerging.Trends@usdoj.gov)
 - Scientific Working Group for the Analysis of Seized Drugs (website: swgdrug.org)

(2) Expand Use of Naloxone and Opioid Use Disorder Treatment

- *Health care providers:*
 - Multiple dosages of naloxone may need to be administered per overdose event because of fentanyl and fentanyl analog’s increased potency relative to other opioids. Orally-ingested counterfeit pills laced with fentanyl or fentanyl analogs may require prolonged dosing of naloxone in the ED hospital setting due to a delayed toxicity that has been reported in some cases [19].
 - Facilitate access to Medication-Assisted Treatment (MAT). MAT is a comprehensive approach to address the needs of persons with opioid use disorder and combines the use of medication with counseling and behavioral therapies. Providers should discuss treatment options with persons who have an opioid use disorder and with persons who have experienced an opioid-

related overdose once they are stabilized. Access to MAT has been demonstrated to be particularly important in the correctional system setting, where recently released persons are known to be at high risk of overdose due to reduced opioid tolerance [16].

- Emergency departments can serve as points of intervention for persons who experience an overdose, and post-overdose protocols, which include prescription of naloxone and connecting patients with case management services or peer navigators to help link them into treatment services are recommended [22].
- *Harm reduction organizations (e.g., organizations, often community-based, focused on reducing the adverse effects of substance use, including overdose, addiction, and infectious disease):*
 - Expand naloxone access to persons at risk for opioid-related overdose and to their friends and family members [23]. Expanded access to naloxone in the correctional setting for those with impending release is important given their elevated risk of overdose upon release [16], and can be best achieved through implementation of naloxone distribution programs that do not require inmates to request special services to receive it [24].
 - Train those using illicit opioids how to effectively administer naloxone and emphasize the importance of calling 911 immediately after recognizing an overdose because available naloxone may be insufficient in reversing the overdose.
 - Link persons misusing opioids to treatment or other services to reduce the risk of overdose.

For More Information

- CDC Opioid Overdose homepage: “Understanding the Epidemic” at <https://www.cdc.gov/drugoverdose/epidemic/index.html>
- CDC Health Advisory: Recommendations for Laboratory Testing for Acetyl Fentanyl and Patient Evaluation and Treatment for Overdose with Synthetic Opioids at <https://stacks.cdc.gov/view/cdc/25259>
- Canadian Centre on Substance Abuse Bulletin: Novel Synthetic Opioids in Counterfeit Pharmaceuticals and Other Illicit Street Drugs at (see CCENDU Bulletin <http://www.ccsa.ca/Resource%20Library/CCSA-CCENDU-Novel-Synthetic-Opioids-Bulletin-2016-en.pdf>).
- MMWR: National Fentanyl Seizures and Changes in Synthetic Opioid-Involved Overdose Deaths –27 States, 2013-2014 (<https://www.cdc.gov/mmwr/volumes/65/wr/mm6533a2.htm>)
- MMWR: Increase in Fentanyl-Related Overdose Deaths — Ohio and Florida, 2010-2015 (<https://www.cdc.gov/mmwr/volumes/65/wr/mm6533a3.htm>)
- MMWR: Characteristics of Fentanyl Overdose – Massachusetts, 2014-2016 (https://www.cdc.gov/mmwr/volumes/66/wr/mm6614a2.htm?s_cid=mm6614a2_e)
- SAMHSA Opioid Overdose Toolkit at: [https://store.samhsa.gov/shin/content/SMA13-4742/Overdose Toolkit 2014 Jan.pdf](https://store.samhsa.gov/shin/content/SMA13-4742/Overdose_Toolkit_2014_Jan.pdf)

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