A 2017-2019 Update on Acute Intoxications and Fatalities from Illicit Fentanyl and Analogs

A 2017–2019 Update on Acute Intoxications and Fatalities from Illicit Fentanyl and Analogues

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The authors report no conflicts of interest related to this work.

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Acknowledgment: The authors would like to thank Annagiulia di Trana and Sara Malaca for technical help.

Funding: The investigation was partially carried out with funding from Presidency of the Ministers Council, Department of Antidrug Policy and from Department of Excellence SBSP, University "Politecnica delle Marche" of Ancona;

Conflict of Interest: None of the authors have any conflict of interest.

Abstract

The aim of this review was to report the most recent cases of acute intoxication, fatalities and "driving under the influence" cases, involving illicit fentanyl and its newest analogues. When available, information on age, sex, circumstances of exposure, intoxication symptoms, cause of death (if applicable) and toxicology results from biological fluid testing was described. Scientific publications reporting fatalities or acute intoxications involving use of fentanyl derivatives were identified from PubMed, Scopus and institutional/governmental websites from January 2017 up to December 2019. The search terms, used alone and in combination, were as follows: fentanyl, street fentanyl, analogues, compounds, derivatives, abuse, fatality, fatalities, death, toxicity, intoxication and adverse effects. When considered relevant, reports not captured by the initial search but cited in other publications were also included. Of the 2890 sources initially found, only 44 were suitable for the review. Emergent data showed that the most common analogues detected in biological samples and seized materials are acetylfentanyl, acrylfentanyl, butyrfentanyl, carfentanil, cyclopropylfentanyl, fluorofentanyl, 4-fluorobutyrfentanyl, 4-fluoroisobutyrfentanyl, furanylfentanyl, 2-methoxyacetylfentanyl, 3-methylfentanyl and ocfentanil. These compounds were frequently administered in association with other illicit substances, medicinal drugs and/or alcohol; patients and the victims often had a previous history of drug abuse. The trend of fentanyl analogues is rapidly evolving with illicit market fluctuations. Since information about potency and lethal dosage are frequently unknown, it is important to identify the new trends for further investigation on therapeutic use, toxicity and fatal doses, and implement public health measures. Recently marketed FAs such as crotonylfentanyl and valerylfentanyl were not involved in intoxications to date, but should be carefully monitored. Many intoxications and fatalities might have gone unnoticed, and research efforts should focus on metabolite identification studies and the implementation of updated and comprehensive analytical methods

Keywords: novel synthetic opioids, illicit fentanyl, fentanyl analogues, fatalities, acute intoxication.

Introduction

Fentanyl is a synthetic opioid analgesic of the phenylpiperidine family; it was originally synthesized in Belgium by Paul Janssen in 1959 (1) as a derivative of meperidine, another synthetic opioid. Like morphine, fentanyl is a μ-opioid receptor agonist in the central nervous system and in heart, lung, vascular and intestinal cells (2) The potency of fentanyl is 50–100 times higher than that of morphine and 25–40 times higher than that of heroin; it has high lipophilicity and easily crosses the blood-brain barrier. Fentanyl was approved for medical use in the United States in 1968. It is commonly used in anesthesia and severe and post-surgical pain management, and is marketed as injectable solutions, transdermal patches, nasal sprays or tablets (transmucosal, effervescent buccal or sublingual) (3). Fentanyl is also used as a heroin-like recreational drug, which quickly gained popularity through its low cost.

Fentanyl analogs (FAs) are structurally and pharmacologically related to fentanyl with minor substitutions. FAs with similar or higher potency than that of fentanyl, such as sufentanil, alfentanil, and carfentanil, have been synthesized in the early 1970s and have been used in anesthesia and research (4). Since they were first introduced onto the pharmaceutical market, fentanyl and analogues have been misused in place of heroin due to cheaper cost. Fentanyl and analogues have been controlled under Schedule I of the 1961 UN Single convention on narcotic drugs since 1964 (5). Since 2012, new FAs started emerging onto the drug market to circumvent toxicological screenings and drug prohibition laws, as a part of the novel psychoactive substance (NPS) trend (6–11). FAs are typically sold as fentanyl substitutes, but have also been sold as heroin or have been found as adulterants in counterfeit prescription drugs. Many cases of overdose and deaths by respiratory depression, cardiac arrest, or severe anaphylactic reaction due to fentanyl and analogue use have been reported (12). Most FAs are not approved for human use, but data on potency and lethal dosage of the most recent substances are frequently unknown (7). The acute and chronic toxicity of many FAs is unknown or has been very sparsely investigated.

Recently, a substantial spike in intoxications due to novel synthetic opioid (NSO) use, and more specifically illicitly manufactured fentanyl and analogues, has been reported, posing a worldwide public health threat (13). In 2017, synthetic opioids (excluding methadone) were involved in more than 28,000 deaths in the United States, which is more than any other type of opioid (14). In the last few years, NSOs have also raised concerns in Europe, Japan, Canada and Australia, due to the multiplication of seizures and the substantial increase in the number of acute intoxications and fatalities (6, 15–17).

In 2017, Pichini (12) et al reviewed the cases of intoxication involving fentanyl and FA use, but no recent systematized data is currently available. It is important to identify the new trends and the most potentially harmful analogues to rapidly implement public health measures and develop relevant methods of detection in biological samples in forensic and clinical toxicology. In this review, we aimed to report the most recent analytically confirmed cases of acute intoxication and fatalities related to FAs and illicit fentanyl.

Methods

Scientific publications reporting fatalities involving use of fentanyl derivatives or other novel synthetic opioids (NSO) were identified from PubMed, Scopus and Institutional/government websites from January 2017 to December 2019. The search terms, used alone or in combination, were as follows: fentanyl, street fentanyl, analogues, compounds, derivatives, abuse, fatality, fatalities, death, toxicity, intoxication and adverse effects. When considered relevant, reports not captured by the initial search but cited in other publications were also included.
Included publications met the following criteria: 1) articles written in English; 2) describing human exposure to illicit fentanyl and/or one or more FAs; 3) confirming exposure through analytical toxicology testing; 4) death or intoxication had to be attributed to illicit fentanyl or one or more FAs either alone or in combination with other substances. All sources were screened independently by three of the authors to determine their relevance in the framework of the current report and selected for inclusion by two of the authors.

Results

Fentanyl and novel synthetic opioid intoxications and fatalities

Of the 2890 sources initially found, only 44 were suitable for the review. Table I summarizes the articles describing acute and fatal intoxications from fentanyl and FA use reported from 2017 to 2019. The parent drugs and metabolites of fentanyl and illicit analogues detected in biological matrices in cases of intoxication and fatalities are reported in Table II. The molecular structures of fentanyl and analogues involved in drug-related fatalities and intoxications is reported in Figure 1. As observed in many drug-related deaths, poly-drug use is frequent. Most victims were young males, although female victims have also been reported, often with a previous history of drug abuse. During the last three years, in Europe, acute intoxications and deaths related to fentanyl and its analogues, alone or in combination with other drugs of abuse, were mostly reported in Sweden and, to a lesser extent, in Germany, Norway, Denmark, Estonia, England, Italy, Latvia, Czech Republic and France (18–32). Between 2018 and 2020, in Canada, fewer than one thousand

fatalities involving fentanyl and its analogues, also in combination with other drugs of abuse, have been reported, mostly in Alberta and Ontario (33, 34). In eastern countries, only a couple of fatalities involving fentanyl and acetylfentanyl were reported in Japan and Australia (35, 36). At the same time, in the United States, fatal cases and intoxications related to illicit fentanyl and its analogues, as a single substance or combined with other drugs of abuse, were reported in Ohio (mainly in Cuyahoga county) and, to a lesser extent, in Massachusetts, Missouri, Oklahoma, Rhode Island and West Virginia (6, 37–45)

Acetylfentanyl

Acetylfentanyl (Figure 1) (N-(1-phenethylpiperidin-4-yl)-N-phenylacetamide) is an opioid analgesic with a threefold-lower potency than that of fentanyl (6).

Acetylfentanyl is particularly prevalent in the U.S. (37–42, 46, 47) and Canada (34) where hundreds of cases of intoxication and fatalities were reported between 2017 and 2019. In the U.S., all cases were reported in eastern states from Maine to Florida. In 2017, O'Donnell et al. described 147 acetylfentanyl-related overdose deaths that occurred in July–December 2016 in 10 American states, representing 2.9% of total opioid-related fatalities (42) Acetylfentanyl was the main cause of death in 23.8% (n = 377) of 1583 overdose cases reported in Marion County from January 1, 2010, through April 30, 2017 (41). Interestingly, in 2018, Griswold et al studied illicit fentanyl use in 30 patients admitted to the emergency department after heroin overdose in New England, U.S., between August and December 2016, and compared self-reported use versus urine drug testing results. All participants reported heroin use but none of them reported using fentanyl prior to Emergency Department presentation. However, acetylfentanyl was identified and quantified in nine urine samples (30%) by liquid chromatography–quadrupole time-of-flight mass spectrometry (LC–QTOF-MS), which may indicate the use of adulterated or counterfeit products(37). Acetylfentanyl was less popular in Europe, where 60 cases involving acetylfentanyl and cyclopropylfentanyl (CyF) (6) and a single fatal case was reported in Western Australia (36).

Acetylfentanyl concentrations ranged from < 1 to 6.39 ng/mL in blood samples (40, 46), and was detected in the liver of a post mortem case at 3.0 mg/kg (blood concentration was 400 ng/mL) (36). Acetylfentanyl's metabolite, acetyl norfentanyl, may be detected to confirm exposure (36).

Acrylfentanyl

Acrylfentanyl (N-(1-phenethylpiperidin-4-yl)-N-phenylacrylamide), also known as acryloylfentanyl (Figure 1), is a FA that was first reported to the United Nations office on drugs and crime (UNODC) early warning advisory (EWA) in 2016, in Asia and Europe (25).

Butler et al. (47) recently reported the first detection of acrylfentanyl in peripheral blood in three cases of intoxication. Qualitative identification was performed by GC–MS and quantification was performed by LC–MS-MS. The concentrations ranged from 0.30 to 0.95 ng/mL.

Butyrfentanyl

Butyrfentanyl (Figure 1), also known as butyrylfentanyl, is less potent than fentanyl, although it has been involved in several fatalities across the United States and European countries (6, 48–59).
In 2018, Muller et al (19) described a fatal intoxication related to butyrfentanyl that occurred in Germany. The intoxication was analytically confirmed and butyrfentanyl was identified by GC–MS and quantified in serum and urine by LC–QTOF-MS. Serum butyrfentanyl concentration was 1 ng/mL, but cyclopropylfentanyl, acetylfentanyl and 4-ANPP were also detected. The same year, butyrfentanyl was found in 13 of 25 FA-related fatalities from January to May 2017 in the north of England (24).

Carfentanil

This opioid (Figure 1) is several hundreds of times more potent than fentanyl and is primarily used as an incapacitating agent for large animals (52). It has been one of the most harmful FAs for several years in North America (33, 34, 37, 40, 42, 46, 53–55).
In 2016, Ohio, U.S., was exceptionally strongly hit by carfentanil with a record of fatal intoxications (53). Between July and December 2016, carfentanil was reported as the principal cause of opioid-related deaths in 354 fatalities in the state of Ohio and as contributory cause in 35 fatalities in the state of West Virginia, U.S. (42). Carfentanil was frequently detected in combination with other illicit substances, as reported by Papsun et al. (55). Between October 2016 and April 2017, carfentanil exposure was confirmed in 355 fatal intoxications that occurred in the states of Michigan, Florida, Ohio and other states at the east of the Mississippi river; other opioids were involved in 48% cases, mainly morphine and/or fentanyl, and 6-acetylmorphine (6-MAM) was detected in 10% cases (55).
Carfentanil was quantified in blood samples from “Driving Under the Influence of Drugs” (DUID) cases, with concentrations ranging from 0.012 to 1.4 ng/mL (53, 55). In fatal cases, peripheral blood concentrations ranged from 0.011 to 2000 ng/mL. Interestingly, blood concentrations could be low in many fatal cases, although carfentanil overdose was identified as the sole cause of death.
In 2017, Schueller et al reported 14 deaths associated with carfentanil use, in which carfentanil concentration in urine ranged from 0.015 to 0.097 ng/mL (0.011 to 0.535 in femoral blood) (53). In

another study, carfentanil urine concentration ranged from 0.03 to 12.2 ng/mL in 12 postmortem cases (blood concentrations ranged from 0.021 to 4 ng/mL) (24).

Cyclopropylfentanyl (CyF)

Cyclopropylfentanyl (CyF) (Figure 1) is a 4-anilidopiperidine analogue with a cyclopropanecarboxamide group substituting fentanyl's propionamide (56). Intoxication cases with serious adverse events associated to CyF exposure occurred in EU in 2017 (56).

Three cases of severe opioid intoxication were treated at the Emergency Department of the University Medical Centre Göttingen, in Germany, between July 2017 and December 2017; all patients survived after appropriate emergency treatment. CyF was quantified in serum in two cases, with CyF concentrations of 51 and 76 ng/mL (19). A series of 13 fatalities was reported in Sweden (32) .

CyF emerged onto the American illicit drug market later, in summer of 2017, and was already involved in many fatalities (38, 57–59). Between December 2017 and May 2018, CyF was quantified in five postmortem cardiac blood samples with concentrations ranging from 5.6 to 82 ng/mL (57). Between June and August 2017, 32 fatalities were reported in Florida, Tennessee, Michigan and Illinois, U.S. Postmortem blood samples were positive for CyF, with mean (± SD) and median concentrations of 15.3 (± 11.9) and 12.3 (range: 1.4–43.3) ng/mL, respectively (58). Fogarty et al reported similar blood concentrations in five additional fatalities (59).

2-, 3-, 4-Fluorofentanyl

The positional isomers *ortho*-, *meta*- and *para*-fluorofentanyl, also named 2-, 3- and 4-fluorofentanyl, respectively, are fentanyl derivatives with a fluorine atom located at the *N*-phenyl moiety (49) (Figure 1).

In 2017, three deaths occurred in Germany after ingestion of unknown pills and powders. Toxicological analysis was performed by LC–MS-MS and high concentrations of 4-fluorofentanyl was found in the femoral blood of two of the victims (25-35 ng/mL) and the bile of one victim (300 ng/mL) (22). The same year, in Norway, two young males were hospitalized with acute intoxication after snorting a white powder that they believed to be a central stimulant. 2-Fluorofentanyl was quantified in one patient with a concentration of 2.5 ng/mL. A few days later, one of the patients was found dead at home and whole blood and urine concentrations were 2.4 and 3.9 ng/mL, respectively (21).

4-Fluorobutyrfentanyl (4F-BF)/4-Fluoroisobutyrfentanyl (4F-iBF)

4-Fluorobutyrfentanyl (4F-BF) is a butyrfentanyl derivative with a fluorine atom located at the *N*-phenyl moiety. 4-Fluoroisobutyrylfentanyl (4F-iBF) (Figure 1) is a 4F-BF position isomer, in which the propyl group is replaced by an isopropyl. The two substances are closely related structurally, and they share the same molecular formula and molecular mass (50).

4F-iBF was identified as the cause of death in three fatalities and a contributing cause of death in 55 fatalities (poly-drug intoxications) between 2014 and 2017 in Miami-Dade County, Florida. Toxicological analyses were performed on postmortem blood samples by LC–MS-MS. 4F-iBF concentrations ranged from 30.6 to 91.7 ng/mL in cases in which it was identified as the sole cause of death (46). 4F-iBF was also detected in two CyF-related deaths and one CyF-related acute intoxication, with concentrations of 18 (blood) (58), 38 (blood) (59) and 7.9 (serum) ng/mL (19), respectively.

Six 4F-BF-related deaths that occurred from 2016 (n = 5) to 2017 (n = 1) in Central New York were described by Vohra et al. (38).

Furanylfentanyl (FuF)

Although furanylfentanyl (FuF) (Figure 1) is five time less potent than fentanyl (52), it was involved in many acute intoxications and deaths, predominantly in the U.S. (24, 34, 38, 42, 54, 55). Papsun et al. reported two acute intoxications that occurred in 2017, in which FuF was found in combination with carfentanil. FuF blood concentrations were 0.14 and 1.1 ng/mL, respectively (55). In another study from 2017, FuF was detected in 182 opioid overdose deaths that occurred in Eastern U.S., representing 3.2% of total opioid overdose fatalities testing positive for FAs and U-47700 (42). Peripheral blood concentrations in fatal cases ranged from 0.52 to 610 ng/mL (46, 47, 54, 58) and FuF cardiac blood concentration was reported in one case at 2.8 ng/mL (peripheral blood concentration was 1.9 ng/mL) (60).

4-Methoxyacetylfentanyl

Methoxyacetylfentanyl (Figure 1) (2-methoxy-N-phenyl-N-[1-(2-phenylethyl) piperidin-4-yl]acetamide) is one of the newest illicit opioids emerging onto the heroin market (61).

Fogarty et al described 42 fatal cases in U.S. involving fentanyl analogues from June to August 2017: 11 from Florida, 12 from Tennessee, 8 from Michigan and 11 from Illinois. In 11 cases, methoxyacetylfentanyl was detected with mean (±SD) and median blood concentrations of 17.7 ± 11.4 ng/mL and 15.1 ng/mL, respectively, and a range of 0.21–39.9 ng/mL; the concentration was below the limit of quantification in three cases (58). Two additional fatal cases were reported in Central New York (38).

3-Methylfentanyl (3-MF)

3-Methylfentanyl (3-MF) (Figure 1) was first synthesized by an industrial chemist in Pittsburgh (51) and is up to 6000 times more potent than morphine. It was identified in "China White" in 1990, as a more potent alternative to α-methylfentanyl**,** which was responsible for an epidemic of deaths in the 1970s (51, 62)

Sofalvi et al. (40) reported a fatal case involving 3-MF use in United States in 2017. The substance was quantified by LC–MS-MS in femoral blood (1.7 ng/mL), heart blood (2.6 ng/mL) and vitreous humor (0.65 ng/mL). Another fatal case was reported by Schueler et al, which occurred in Cuyahoga County, Ohio, U.S., with a similar antemortem blood concentration (53).

Ocfentanil

Ocfentanil, or N-(2-fluorophenyl)-2-methoxy-N-[1-(2-phenylethyl)piperidin-4-yl]acetamide (Figure 1), also called A-3217, was patented in 1986 and evaluated in humans in 1989; it was subsequently not approved for medical use (31, 63).

Three ocfentanil-related deaths and a series of three intoxications occurred in France in 2017 (26). Ocfentanil blood concentrations in fatal cases were 3.7, 11.6 and 5.3 ng/mL in cases 1, 2 and 3, respectively; ethanol, medicinal drugs and drugs of abuse were additionally found. In the case series of three intoxications, caused by nasal insufflation of capsules containing ocfentanil, blood concentrations varied from 13.9 to 35.2 ng/mL. Another fatal case was reported in 2018 in Italy (31); ocfentanil concentrations were reported in femoral blood, cardiac blood, urine, bile, brain, liver, kidney and lung.

Discussion and Conclusion

In the last few years, latest health protection policies, efficient national early warning systems and fluctuations of the illegal drug market have modified the trends of consumption of illicit fentanyl and related compounds. New substances are emerging from the clandestine market to bypass laws and analytical detection (64). Fentanyl and analogs are mainly responsible. Information about their potency and toxic and lethal dosage is frequently unknown.

In 2017, NSOs were involved in more than 28,000 overdose fatalities in the U.S., which impacted the demographics of opioid-related overdose fatalities, traditionally associated with heroin and methadone (14). This "epidemic" has been dominated by fentanyl and analogues, which represented 59.8% of opioid-related overdoses in 2017, but other NSOs such as U-47700 were also responsible for many deaths (14). In the same period of time, fentanyl and analogues were involved

in more than 11,000 opioid-related deaths in Canada (34). Acetylfentanyl, FuF and carfentanil were already well-established prior to 2017 (12) and keep being detected in post-mortem and ante-mortem samples in the United States and Canada in more recent cases (33, 34, 37, 38, 40–42, 46, 47, 53–55, 60, 65) CyF and 4-methoxyacetylfentanyl recently emerged onto the drug market, but have already been involved in many fatalities (34, 38, 58, 59), which constitutes a remarkable evolution compared to the review of Pichini et al on FA-related intoxications and fatalities reported before 2017 (12). Fatalities involving acrylfentanyl, butyrfentanyl, fluorobutyrfentanyl, fluoroisobutyrfentanyl, 3-MF and methylfentanyl were also reported (34, 38, 40, 42, 47, 53, 59). In the European Union, around 50 NSOs have been reported to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) early warning system on new psychoactive substances over the last three years (30). CyF, carfentanil, acryloylfentanyl and 2-methoxyacetylfentanyl, in particular, have been associated with a large number of deaths and acute intoxications (19, 21, 23), especially in northern countries such as Sweden (32, 56, 61), Germany (18–20, 28, 30) and England (24). Ocfentanil is among the most recent FAs on the drug market and was involved in four fatalities since 2017 (26, 31), although the consequences of ocfentanil use are not as important as those of CyF and 4-methoxyacetylfentanyl, careful monitoring of the newest substances is a necessity. Similarly, little is known about other recent FAs, such as crotonylfentanyl and valerylfentanyl, and these substances were not involved in any cases of acute intoxication or fatalities to date. Interestingly, only two fatal intoxications were reported in Japan (35) and Australia (36) between 2017 and 2019. These intoxications were due to fentanyl and acetylfentanyl, respectively, always in association with other medical drugs (e.g., sertraline, promethazine and benzodiazepines) or drugs of abuse (amphetamine). Even if FAs are generally first synthesized in Asia (mostly China), many more cases of acute intoxication and fatalities involving illicit fentanyl were reported from North America and the European Union. These discrepancies may have several origins: 1) FAs may be synthesized and directly marketed in EU and USA; 2) FA intoxications might be not properly identified (e.g., confusion with heroin overdose without analytical confirmation, analytical methods not adapted); 3) FA intoxications might be not properly reported or were reported in languages other than English and were not retrieved by our literature search. Illicit fentanyl and analogues are causing a harmful public health threat particularly involving people with previous history of drugs and alcohol abuse. Victims of intoxication to fentanyl and analogues are typically male of all ages, and almost all reports involved co-exposure to other opioids, benzodiazepines, drugs of abuse or cannabinoids.

Although many cases of intoxication and fatalities due to fentanyl and analogues were reported, the number of FA-related cases may be underestimated, as they are likely taken in combination with

other opioids and may be unnoticed, and low active concentrations in biological samples are challenging to detect (64, 66, 67). To improve detection, more effort should be done on metabolite identification studies to identify the most relevant markers of FA exposure, and the development of updated analytical methods based on these metabolite identification studies and recent trends. Additionally, new cases of exposure to FAs and seizure should be systematically reported to early warning systems to obtain a clear, comprehensive and updated list of new emergent substances, considering the rapid evolution of the illicit market.

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figure caption

Figure 1. Molecular structures of fentanyl analogues involved in drug-related fatalities and intoxication.

Table I. Case Reports of Acute Intoxications and Fatalities from Illicit Fentanyl and Analogues							
Illicit fentanyl and analogues	**Co-exposure**	**Number of acute intoxications and symptoms**	**Number and cause of deaths**	**Age, Sex**	**Country and/or State**	**Year**	**Ref.**
EUROPE							
Acetylfentanyl, Cyclopropylfentanyl	–	–	60 fatalities	55 M (median age 32, range 21–59), 5 F (median age 30, range 25–39)	Sweden (59), Norway (1)	2017	6
Acrylfentanyl	Amphetamine, Benzodiazepines, Buprenorphine, 4-Cl-α-PPP, N-Ethylhexedrone, 4-Methylphenidate, Oxycodone	21 intoxications with respiratory depression, miosis, vomiting, tachycardia, anxiety, low oxygen saturation, hypertension, cyanosis, blurred vision, somnolence, tiredness, high body temperature, chest pain & hallucinations	–	18 M (mean age 35, median 29, range 22–51), 3 F (mean age 28, median 22)	Sweden	March–August 2016	6
Fentanyl	Ethanol	–	242 fatalities by fentanyl overdose	82% M, 18% F (mean age ± SD 35 ± 9)	Germany	2005–2014	18
4-ANPP, Butyrfentanyl, Cyclopropylfentanyl, 4-Fluorobutyrfentanyl	U-47700	3 intoxications with loss of consciousness, tremor & traumatic forehead laceration, bradypnea, bradycardia & arterial hypotension	–	M (age range 30–35)	Germany	2017	19

o-Fluorofentanyl	Alprazolam, Amphetamine, Benzoylecgonine, Ethanol, GHB, Paracetamol, THC	1 intoxication with miosis & low oxygen saturation	1 fatality by combined drug intoxication	2 M	Norway	2017	21
Fluorofentanyl	3,4-DMMC, Amitriptyline, Amphetamine, Caffeine, Heliomethylamine, Nicotine, Nordiazepam, Opipramol, THC-COOH	Patients were unresponsive	3 fatalities by combined drug intoxication	2 M (age range 26–34), 1 F (33)	Germany	2017	22
Acryloylfentanyl, 4-Chloroisobutyrfentanyl	–	9 intoxications with decreased consciousness, respiratory depression, miosis, tachycardia & hypertension	–	Age range 23–51	Sweden	March-October 2016	23
Acryloylfentanyl 4-Chloroisobutyrfentanyl, Fluoroisobutyrfentanyl	Amphetamines, Antidepressants, Antipsychotics, Benzodiazepines, Buprenorphine, Cannabinoids, Ethanol, Gabapentin, Hydrocodone, Oxycodone, Pregabalin, Synthetic cathinones, Zopiclone	Patients were unresponsive	47 fatalities by combined drug intoxication	86% M (age range 19–54), 14% F (age range 29–50)	Sweden (43 cases), Estonia (3), Denmark (1)	2016	23
Butyrfentanyl, 4F-Butyrfentanyl, Carfentanil, Fentanyl, Furanylfentanyl	Alprazolam, BEG, Cocaine, Codeine, Diazepam, Duloxetine, Ethanol, Gagapentin, Methadone, Mirtazapine, Morphine, Olanzapine, Pregabalin, Sertraline, THC, THC-COOH, Zopiclone	Patients were unresponsive	25 fatalities by combined drug intoxication	22 M, 3 F (age range 21–54)	England	January–May 2017	24
Ocfentanil	Case 1: Acetaminophen, Caffeine, Ethanol; Case 2: 6-MAM, Morphine; Case 3: Cannabis, Cocaine, MDMA	3 intoxications (symptoms not reported)	3 fatalities by combined drug intoxication	–	France	May 2017	26
Methoxyacetylfentanyl	–	–	6 fatalities	5 M (mean age 34.8, median 34, range 28-41), 1	Sweden	December 2016–June 2017	30

				F (28)			
Ocfentanil	–	Patient was unresponsive	1 fatality by opioid intoxication	M (39)	Italy	2017	31
Cyclopropylfentanyl	–	–	13 fatalities	–	Sweden	2019	32
CANADA							
Carfentanil, Fentanyl	Alcohol, Antidepressants, Antiepileptics, Antihistamines, Benzodiazepines, Buprenorphine, Cocaine, Codeine, Heroin, Hydromorphone, Methadone, Methamphetamine, Morphine, Oxycodone, Tramadol	–	653 fatalities by opioid overdose	77% M, 23% F (median age 38.1, range 15–72)	Alberta	2017	33
Acetylfentanyl, Acrylfentanyl, Butyrfentanyl, Carfentanil, Cyclopropylfentanyl, Fentanyl, Fluoroisobutyrfentanyl, Furanylfentanyl, 3-Methylfentanyl	–	–	716 fatalities	76% M, 24% F	Ontario (459), British Columbia (299 cases), Alberta (159), Quebec (119), Nova Scotia (13), Saskatchewan (12), Foundland (9), New Brunswick (6), Manitoba (4), New Yukon (1)	January–March 2019	34
U.S.							
Acetylfentanyl, Carfentanil, Fentanyl	6-MAM, Benzodiazepines, Buprenorphine, Codeine, Methadone, Morphine, U-44770	30	Heroin overdose	45.4% M, 54.6% F (median age 20)	Maine, Vermont, New Hampshire, Massachusetts, Rhode Island, Connecticut	August 24, 2016 & December 11, 2016	37
Acetylfentanyl, Cyclopropylfentanyl, Fentanyl, Fluorobutyrfentanyl, Furanylfentanyl, Methoxyacetylfentanyl	–	–	417 fatalities	83% M, 17% F (mean age 39)	Central New York (Cayuga, Madison, Oneida, Onondaga & Oswego counties)	January 2013-December 2017	38

Acetylfentanyl, Carfentanil, Fentanyl, 3-Methylfentanyl	6-MAM, 7-Aminoclonazepam, 11-OH-THC, Clonazepam, Codeine, Cyclobenzaprine, Diazepam, Diphenhydramine, Meprobamate, Morphine, Naloxone, Nicotine, Nordiazepam, Norpseudoephedrine, Pseudoephedrine, Oxazepam, Temazepam, THC, THCA	–	64 fatalities	–	Ohio	July 2016	40
Acetylfentanyl, Fentanyl	Codeine, Heroin, Hydrocodone, Hydromorphone, Morphine, Oxycodone, Oxymorphone	–	377 fatalities by drug overdose	64.1% M, 35.9% F (mean age 40.2)	Indiana (Marion County)	January 1, 2010–April 30, 2017	41
Acetylfentanyl, Acrylfentanyl, Butyrfentanyl, Carfentanil, Fentanyl, *p*-Fluorofentanyl, Furanylfentanyl, 3-Methylfentanyl	Cocaine, Heroin, Metamphetamine, U-44770	–	5152 fatalities by opioid overdose	Age range 15–≥65	Maine, Massachusetts, Missouri, New Hampshire, New Mexico, Ohio, Oklahoma, Rhode Island, West Virginia, Wisconsin	July–December 2016	42
Fentanyl	Other opioids	200 intoxications	Opioid overdose	73% M, 27% F (mean age ± SD 34.0 ± 9.29)	Massachusetts	April & September 2017	43
Fentanyl	–	–	69 fatalities by fentanyl overdose	61% M, 39% F (median age 45)	Rhode Island	January 2012–March 2014	44

Fentanyl	Heroin, Morphine	–	125 fatalities by opioid overdose	100 M, 25 F [age range 15–24 (15 cases), 25–34 (52 cases), 35–44 (24 cases), ≥45 years (34 cases)]	Massachusetts (Barnstable, Bristol & Plymouth)	October 2014–March 2015	45
Case 1: Acrylfentanyl Case 2: – Case 3: Acrylfentanyl, Furanylfentanyl	Case 1: Amphetamine, Methamphetamine, THC-COOH; Case 2: Dihydrocodeine, Hydrocodone, Hydromorphone, Ethanol, Naloxone; Case 3: Hydromorphone, Morphine, Naloxone	Case 1: dead at the scene; Case 2: unresponsive Case 3: unresponsive	3 fatalities by combined drug intoxication	Case 1: M (23); Case 2: M (43); Case 3: M (26)	US	June 2016	46
Carfentanil, 3-Methylfentanyl	–	6 intoxications; Patients were unresponsive	19 fatalities by carfentanil and 3-methylfentanyl intoxication	–	Ohio (Cuyahoga County)	2017	53
Carfentanil, Furanylfentanyl, Norfentanyl	Alprazolam, BEG, Buprenorphine, Caffeine, Codeine, Ethanol, Hydromorphone, Morphine, Naloxone, Norbuprenorphine, Nordiazepam, Oxazepam, Phenytoin, Quetiapine, Temazepam, THC-COOH, Topiramate	Patients were unresponsive or dead	13 fatalities by combined drug intoxication	10 M, 3 F (age range: 26–62)	Indiana (Indianapolis)	July–September 2016	54
Carfentanil, Fentanyl, Furanylfentanyl	6-MAM, Cocaine, Morphine, THC, THC-COOH	4 intoxications; Case 1: unresponsive; Case 2: conscious but under narcotic effect drugs; Cases 3 & 4: not reported	Synthetic Opioid overdose	75% M, 25% F (median age 40, range: 20–70)	Michigan, Florida, Ohio, Pennsylvania, East of the Mississippi River	October 2016-April 2017	55
Cyclopropylfentanyl, Methoxyacetylfentanyl	–	–	42 fatalities by combined drug intoxication	35 M, 7 F (mean age 43)	Florida (11 cases), Tennessee (12), Michigan (8), Illinois (11)	June-August 2017	58

Cyclopropylfentanyl, Fluoroisobutyrfentanyl, Methoxyacetylfentanyl	–	–	5 fatalities by synthetic opioid overdose	3 M, 2 F (Cases 1–3: age not provided, Case 4: 27, Case 5: 25)	New Jersey (1 case), North Carolina (2), Canada (1), Michigan (1)		59
4-ANPP, Furanylfentanyl	Benzodiazepines, Caffeine, Cannabinoids, Cotinine, Methamphetamine, Nicotine	Patient was unresponsive	1 fatal intoxication by combined drug intoxication	M (23)	California (San Francisco)	October 2016	60
East Asia							
Fentanyl	Acetaminophen, Allylisopropylacetylurea, Celecoxib, Estazolam, Promethazine, Sertraline	Congestion and edema	1 fatal intoxication	F (40)	Japan	2019	35
Australia							
Acetylfentanyl	Desmethyldiazepam, Diazepam, Methylamphetamine, Noramphetamine, Promethazine	Bruising of the scalp, congestion and edema	1 fatal intoxication	M (24)	Western Australia	2015	36

3-FPM: 3-Fluorophenmetrazine; 3-MeO-PCP: 3-Methoxyphencyclidine; 4-ANPP: 4-anilino-N-phenethyl-piperidine; 4-BMC: 4-Bromomethcathinone; 4-Cl-α-PPP: 4-chloro-α-pyrrolidinopropiophenone; 4F-MPH: 4-Fluoromethylphenidate; 5-DBFPV: 5-dihydrobenzofuranpyrovalerone; 6-MAM: 6-Monoacetylmorphine; 11-OH-THC: 11-hydroxy-tetrahydrocannabinol; α-PHP: α-Pyrrolidinohexiophenone; α-PNP:α-Pyrrolidinopentiophenone; α-PVP: α-Pyrrolidinovalerophenone; BEG: Benzoylecgonine; F: female; GHB: Gamma-hydroxybutyrate; M: male; MDAI: 5,6-methylenedioxy-2-aminoindane; MDMA: 3,4-Methylenedioxymethamphetamine; MDPHP: 3,4-methylenedioxy-α-pyrrolidinohexanophenone; MDPPP: 3,4-methylenedioxy-α-pyrrolidinopropiophenone; PV8 : α-Pyrrolidinoheptiophenone; SD: Standard Deviation; THC: Δ(9)-tetrahydrocannabinol; THC-COOH: 11-nor-Δ(9) -tetrahydrocannabinol-carboxylic acid; THCA: Δ(9)-tetrahydrocannabinolic acid.

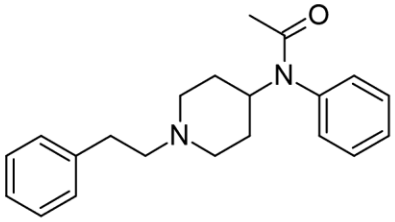
Table II. Parent Drugs and Metabolites of Fentanyl and Illicit Analogues Detected in Different Biological Fluids and Matrices in Case of Intoxications and Fatalities

Ref.	Fenatanyl and FAs	Matrices	Parent drug	Metabolites	
18	Fentanyl	Femoral blood (ng/mL)	Range: 0.1–240	–	
			Mean: 16.9		
			Median: 11.0		
		Heart blood (ng/mL)	Range: 15.0–18.7		
		Liver tissue (ng/mg)	3.7		
		Lung fluid (ng/mL)	20		
		Decomposition fluid (ng/mL)	"High concentration"		
21	*o*-Fluorofentanyl	Serum (ng/mL)	2.5	–	
		Blood (ng/mL)	2.4		
		Urine (ng/mL)	3.9		
22	Fluorofentanyl	Femoral blood (ng/mL)	Range: 25–35	–	
		Bile fluid (ng/mL)	300		
26	Ocfentanil	Blood (ng/mL)	Range: 3.7–35.2	–	
31	Ocfentanil	Peripheral blood (ng/mL)	36.4	–	
		Heart blood (ng/mL)	49.8		
		Urine (ng/mL)	67.9		
		Bile fluid (ng/mL)	365		
		Brain (ng/g)	72		
		Liver (ng/g)	106		
		Kidney (ng/g)	75.5		
		Lung (ng/g)	108		
32	Cyclopropylfentanyl	Urine	N.R.	Norcyclopropylfentanyl [N.R.]	
		Bile fluid (ng/mL)	300		
35	Fentanyl	Femoral blood (ng/mL)	51	Norfentanyl	72
		Heart blood (ng/mL)	33		76
36	Acetylfentanyl	Blood (ng/mL)	400	Noracetylfentanyl [N.R.]	
		Liver (ng/g)	3000		
37	Fentanyl Acetylfentanyl	Urine	N.R.	Norfentanyl [N.R.]	
40	Acetylfentanyl	Heart blood (ng/mL)	7.2	–	
		Femoral blood (ng/mL)	2.2		
		Vitreous humor (ng/mL)	1.3		
	Fentanyl	Heart blood (ng/mL)	<1.0; 35	Norfentanyl	0.53
		Femoral blood (ng/mL)	7.3		0.26
		Vitreous humor (ng/mL)	5.1		–
	Furanylfentanyl	Heart blood (ng/mL)	8.7	–	
		Femoral blood (ng/mL)	5.5		
		Vitreous humor (ng/mL)	30		

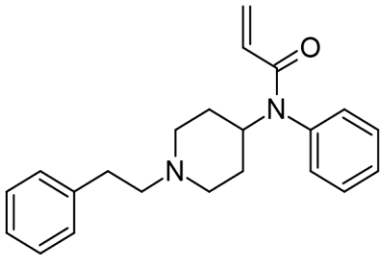
	Methylfentanyl	Heart blood (ng/mL)	2.6	–	
		Femoral blood (ng/mL)	1.7		
		Vitreous humor (ng/mL)	0.65		
	Carfentanil	Heart blood (ng/mL)	1.9	–	
		Femoral blood (ng/mL)	0.36		
		Whole blood (ng/mL)	0.33		
46	β-Hydroxythiofentanyl	Blood (ng/mL)	Range: <1.0–97.1	–	
	Acetylfentanyl		Range: <1.0–6.39		
	Fentanyl		Range: <1.0–46.2		
	Furanylfentanyl		Range:<1.0–59.3		
	Carfentanil		Range: <0.2–8.47		
	p-Fluoroisobutyrfentanyl		Range: <1.0–1567		
47	Fentanyl	Urine (ng/mL)	0.6	Norfentanyl	1.5
	Acrylfentanyl	Peripheral blood (ng/mL)	Range: 0.3–0.95	–	
	Furanylfentanyl		0.95	–	
53	Methylfentanyl	Blood (ng/mL)	1.13	–	
	Carfentanil	Femoral blood (ng/mL)	Range: 0.011–0.535	–	
			Mean: 0.159		
			Median: 0.095		
		Urine (ng/mL)	Range: 0.015–6.842		
			Mean: 1.098		
			Median: 0.367		
		Vitreous humor (ng/mL)	0.025; 0.067		
		DUID Antemortem blood (ng/mL)	Range: 0.012–0.293		
			Mean: 0.114		
			Median: 0.074		
54	Carfentanil	Blood (ng/mL)	Range: 0.01–0.617	Norfentanyl [N.R.]	
	Fentanyl		2.9; 1.1	–	
	Furanylfentanyl		0.61	–	
57	Furanylfentanyl	Blood (ng/mL)	Range: 2.0–42.9	–	
			Mean: 9.7		
			Median: 6.9		
58	Cyclopropylfentanyl	Blood (ng/mL)	Range: 1.4–43.3	–	
			Mean: 15.3 (±11.9)		
			Median: 12.3		
	Methoxyacetylfentanyl		Range: 0.21–39.9	–	
			Mean: 17.7 (±11.4)		
			Median: 15.1		
	Fentanyl		Range: 0.93–22	Norfentanyl	0.31–5.5
	Acrylfentanyl		0.64; 2.1	–	
	Furanylfentanyl		0.52	–	
59	Cyclopropylfentanyl,	Blood (ng/mL)	2.3–130.5	4-ANPP	5.2
	Fluoroisobutyrfentanyl,		38	–	

	Methoxyacetylfentanyl		Positive	–	
60	Furanylfentanyl	Peripheral blood (ng/mL)	1.9	4-ANPP	4.3
		Heart blood (ng/mL)	2.8		5.8
		Urine (ng/mL)	Positive		Positive
		Liver (ng/g)	Negative		>40.0
		Vitreous humor (ng/mL)	<0.20		<0.20
		Gastric content (ng/g)	55000		Negative

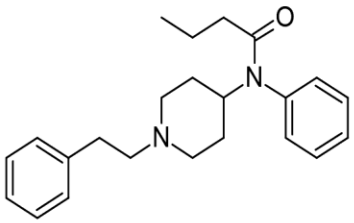
4-ANPP: 4-anilino-N-phenethyl-piperidine; FA: fentanyl analogue ; N.R: not reported.



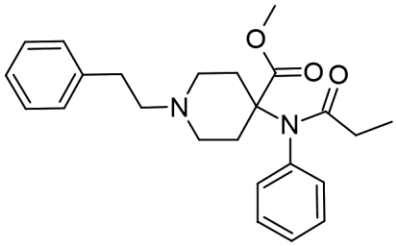
Acetylfentanyl



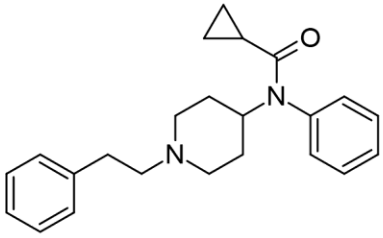
Acrylfentanyl



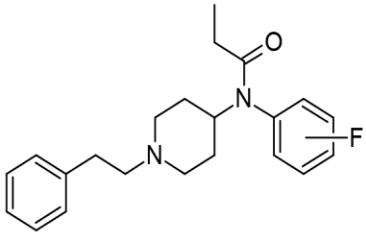
Butyrfentanyl



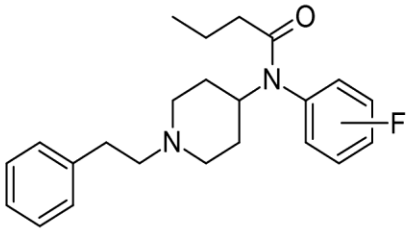
Carfentanil



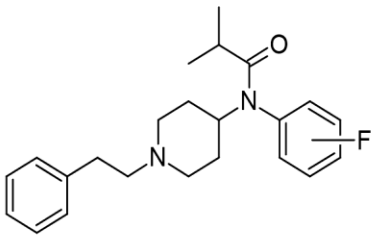
Cyclopropylfentanyl



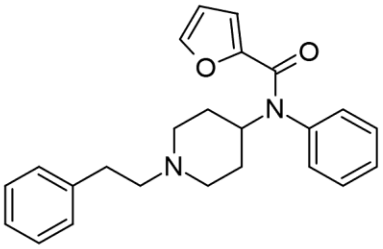
Fluorofentanyl



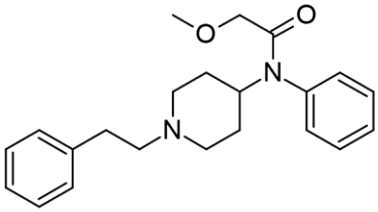
Fluorobutyrfentanyl



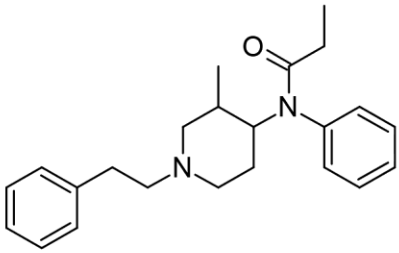
Fluoroisobutyrfentanyl



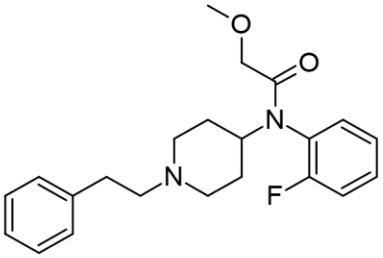
Furanylfentanyl



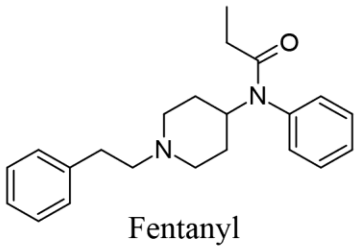
Methoxyacetylfentanyl



3-Methylfentanyl



Ocfentanil



Fentanyl

Fig 1