

Case Series of Novel Illicit Opioid-Related Deaths

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ABSTRACT

Novel illicit opioids, such as furanyl fentanyl and U-47700, are being encountered with increasing frequency in street heroin samples and have been confirmed in a series of overdose deaths in Tennessee. In this paper, we report the pathology and toxicology from 11 deaths involving furanyl fentanyl and U-47700. Routine toxicology was performed on postmortem femoral or antemortem hospital blood samples with targeted broad spectrum drug screening using liquid chromatography-time-of-flight mass spectrometry (LC-TOF/MS). Confirmation and quantitation of the opioid agonists U-47700 and furanyl fentanyl was performed by ultra-high-performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS) using a novel method. Two cases were identified as containing U-47700 in whole blood (189 and 547 ng/mL), and nine cases contained furanyl fentanyl in whole blood, with concentrations ranging from 2.0 – 42.9 ng/mL. In all 11 cases, the manner of death was deemed accident, with drug intoxication being the primary cause of death; one case was complicated by smoke inhalation. All of the decedents were males ranging from 18-62 years, with the median age being 36 years old. The successful identification and confirmation of these novel illicit opioids in this case series relied on the comprehensive investigation and collaboration of scene investigation, forensic pathology, and forensic toxicology. *Acad Forensic Pathol.* 2017 7(3): 477-486

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INTRODUCTION

Within the past few years, there has been an increase in drug-related overdoses caused by novel illicit opioids across the US (1, 2). The trend is believed to have been fueled by an increased demand for heroin, the availability of other prescription painkillers like oxycodone, and the expansion of the research for chemical or novel psychoactive substance (NPS) movement, which has expanded from synthetic cannabinoids and cathinone-derived stimulants, to include novel potent opioid agonists (3–5) and benzodiazepines (6). These developments have opened up additional opportunities for recreational drug use while circumventing routine toxicology testing and evading scheduling legislation. The novel illicit opioids include compounds culled from pharmaceutical research patents and pharmaceutical company catalogs from initiatives in finding alternatives to morphine and by chemically tweaking popular analgesic drugs like fentanyl. The first fentanyl analog to achieve recreational popularity was acetyl fentanyl (7, 8), followed by butyryl fentanyl (9–12). Novel compounds sourced from pharmaceutical research that have been implicated in fatalities include MT-45 (4, 13) and AH-7921 (5, 14–17). Structures of these and related compounds are shown in **Figure 1**.

Beginning in 2015 and continuing through 2016, two of these novel opioids, furanyl fentanyl and U-47700 (**Figure 1**), were encountered in postmortem toxicology casework in Tennessee, with the first case

being encountered in May 2015. Furanyl fentanyl (N-(1-(2-phenylethyl)-4-piperidinyl)-N-phenylfuran-2-carboxamide, “Fu-F”) is a fentanyl derivative that differs from fentanyl in that it has a furanyl ring in place of the methyl group adjacent to the carbonyl bridge (**Figure 1**). Furanyl fentanyl has a median effective dose, or ED₅₀, in mice of 0.02 mg/kg (18), which is comparable to that of fentanyl (0.016 mg/kg) (19). The second chemical, U-47700 (trans-3,4-dichloro-N-(2-(dimethylamino)cyclohexyl)-N-methylbenzamide) (**Figure 1**) is an opioid analgesic drug developed by the pharmaceutical company Upjohn in the 1970’s that has a structure unrelated to morphine; however, it is a structural analog of AH-7921, an earlier experimental opioid agonist developed by the drug company, Allen and Hanbury, that has been implicated in earlier referenced fatalities (20). U-47700 is a selective μ -opioid receptor agonist and in animal models has been demonstrated to have approximately 7.5 times the potency of morphine (21, 22), while fentanyl has a potency of 50 to 100 times that of morphine.

As with most of these novel illicit opioids, the effects of U-47700 and furanyl fentanyl have not been studied in humans. However, based on preclinical testing, the compounds are expected to produce effects similar to those of other opioid agonists, such as analgesia, sedation, euphoria, and respiratory depression. Naloxone has proven to be an appropriate antidote in overdoses related to U-47700, which further supports the proposition that U-47700 is an opioid receptor agonist

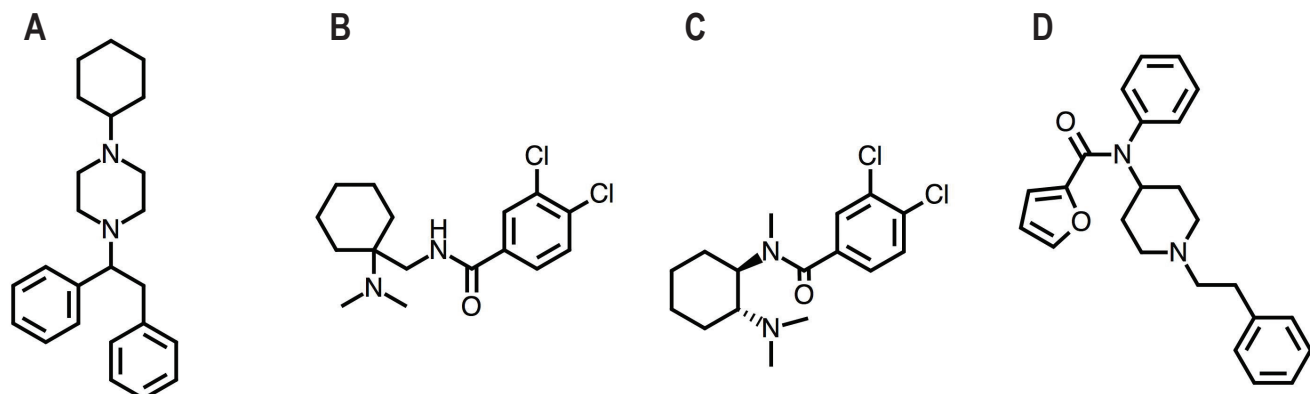


Figure 1: Structure of **A)** MT-45, **B)** AH-7921, **C)** U-47700, **D)** furanyl fentanyl.

(23). There have been several recent reports of deaths associated with both furanyl fentanyl and U-47700 (3, 23–26). These deaths typically appear as routine intravenous drug deaths with drug paraphernalia found at the scene and indicators at autopsy including pulmonary edema, which is frequently seen in opioid deaths. Due to the lack of clinical data, case series of human intoxications and fatalities help to provide critical information to the scientific community.

Throughout 2016, a number of case reports involving both novel illicit opioids emerged, highlighting the danger these substances pose. Subsequently, U-47700 and furanyl fentanyl were scheduled by the US Drug Enforcement Administration (DEA) in November of 2016 (27, 28). Despite domestic efforts to control these compounds, they continue to be implicated in drug-related deaths. China recently listed the intention of controlling the export of furanyl fentanyl, along with carfentanil, valeryl fentanyl, and acryl fentanyl as of March 2017 (29). It is unknown at this time what the effect that ban will have on the availability of these compounds in the US.

METHODS

Specialized toxicological testing for furanyl fentanyl and U-47700 was pursued in a set of 11 cases from Tennessee in which there was an indication of a novel illicit opioid from scene investigation and/or preliminary testing did not reveal the presence of a suspected opiate.

In nine of the 11 cases, femoral blood was collected in gray top tubes during forensic autopsies performed in suspected drug deaths. One additional case was submitted as an antemortem peripheral blood specimen in a blue top vial and a second case was submitted as hospital blood in a light blue top vial. Blue and light blue top tubes with a citrate preservative are typically specimen containers for diagnostic tests; however, these samples become evidentiary if an individual dies in the hospital during treatment, which occurred in these two cases. Blood specimens were stored refrigerated and then transferred to the laboratory for toxicological analysis.

Toxicological Screening of Postmortem Samples

Routine drug screening for over 330 common prescription and recreational drugs using enzyme-linked immunosorbent assay (ELISA) for salicylates, barbiturates, and cannabinoids, and liquid chromatography time-of-flight (LC-TOF) mass spectrometry was performed. A volatiles screen for ethanol, methanol, acetone, and isopropanol was also performed using headspace gas chromatography with flame ionization detection (HS-GC/FID). Additional supplemental testing for drugs outside the scope of the screening analysis was undertaken when requested. All positive findings in the screen were subsequently confirmed and quantitated using validated liquid chromatography tandem mass spectrometry (LC-MS/MS) methods.

In two of the 11 cases, plastic bags labeled as “U-47700” were located during scene investigation (**Images 1 and 2**), which was helpful in prompting additional analysis. Fortunately, the plastic bags were labeled appropriately with its correct contents as verified by toxicology testing; it is not uncommon for substances distributed on the black market to have missing, incorrect, or misleading information on their packaging. Specialized testing for U-47700 and furanyl fentanyl was pursued upon request of the medical examiner using a *de novo* method previously described (3).

RESULTS

Blood samples from 11 cases relating to deaths involving furanyl fentanyl and/or U-47700 were submitted for quantitative analysis for U-47700 or furanyl fentanyl. These deaths occurred between May 2015 and October 2016. **Table 1** details the specifics of the 11 cases.

DISCUSSION

This report details a series of 11 deaths from Tennessee where novel illicit opioids U-47700 and furanyl fentanyl were implicated in toxicology findings and considered causative in the deaths. Two cases were positive for U-47700, with concentrations of 547 and 189 ng/mL in femoral blood. Nine other cases

were positive for furanyl fentanyl, with concentrations ranging from 2.0 to 42.9 ng/mL and an average concentration of 9.7 ng/mL (median 6.9 ng/mL). All manners of death were classified as accident. These concentrations are consistent with quantitative results previously reported by the authors (U-47700, 17-490 ng/mL; furanyl fentanyl, 2.5-76 ng/mL) (3).

Opiates have, over the course of time, been among the most frequently encountered substances in drug-related deaths (30–34). In recent years, deaths related to NPS such as 5-IT (35, 36), methylene (37–39), methoxetamine (40), methylenedioxypropylamphetamine (MDPV) (41), methedrone (42), and para-methoxymethamphetamine (PMMA) (43) have been previously reported. Other NPS have previously been reported in Tennessee (44), but this is the first published postmortem case series from the state involving novel illicit opioids. Deaths caused by NPS continue to be

a problem for death investigators, medical examiners, and toxicology laboratories. Identification of the causal agents typically involves extensive additional investigation and often requires development and on-the-fly validation of new toxicological assays if and when certified standard reference materials are available, which can often lag the casework findings by weeks or months. In addition, as demonstrated by this case series, the autopsy findings (e.g., pulmonary edema and histologic evidence of polarizable material in the lungs) in deaths caused by NPS are nonspecific and similar to those seen in deaths due to other drugs.

Scene investigation is extremely important for all potential drug-related deaths. The successful identification of pertinent substances in toxicology, especially those considered to be NPS, typically require additional targeted testing. Often, this targeted testing is dependent solely on investigative information from

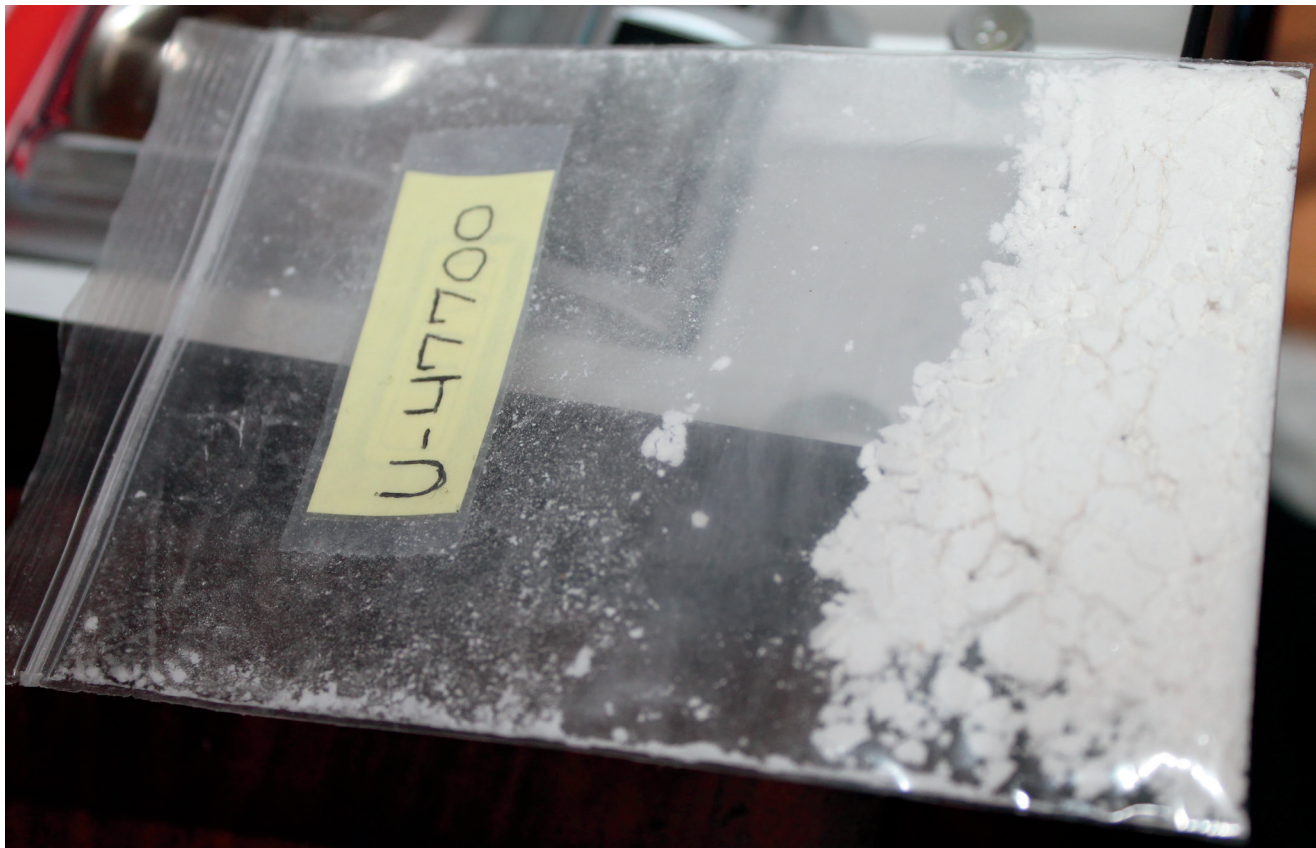


Image 1: Plastic baggie labeled U-47700 containing white powder.

the scene, and requires the appropriate communication between scene investigators, medical examiners, forensic pathologists, and toxicologists to ensure the appropriate testing is completed. In several of the cases described here, baggies of drugs were collected at the scene or found in the decedent's possession; these appropriately labeled products helped to alert the medical examiner to request specialized toxicological testing, since most newer substances would not be covered under routine toxicology testing. Specialized toxicological testing for novel illicit opioids is also recommended in suspected opiate overdose cases when routine testing does not confirm the presence of any causative agents. Positive but unconfirmed fentanyl screens may provide some insight into the presence of a fentanyl derivative such as furanyl fentanyl, since many of the fentanyl derivatives have some degree of cross-reactivity with fentanyl targeted immunoassays (45).

All 11 cases reported were positive for at least one other substance, and polysubstance abuse cases involving NPS are always difficult to interpret since little information is available regarding toxicity of individual substances. Of the 11 reported cases, six included other opioids, and two of those cases reported 6-monoacetylmorphine (6-MAM) in vitreous. It could not be determined in either case if the furanyl fentanyl detected was a concomitant exposure with the heroin, or if the drugs were taken at separate times. In Case 5, in addition to the detection of morphine in blood and 6-MAM in vitreous, the cocaine metabolite benzoylecgonine was detected, and since the blood was collected in a blue top tube, the sample lacked the proper preservative to inhibit the degradation of cocaine to its inactive metabolite. Furanyl fentanyl has been found as a contaminant in crack cocaine in a series of overdose events in British Columbia (46). There was no apparent pattern of polysubstance abuse among these

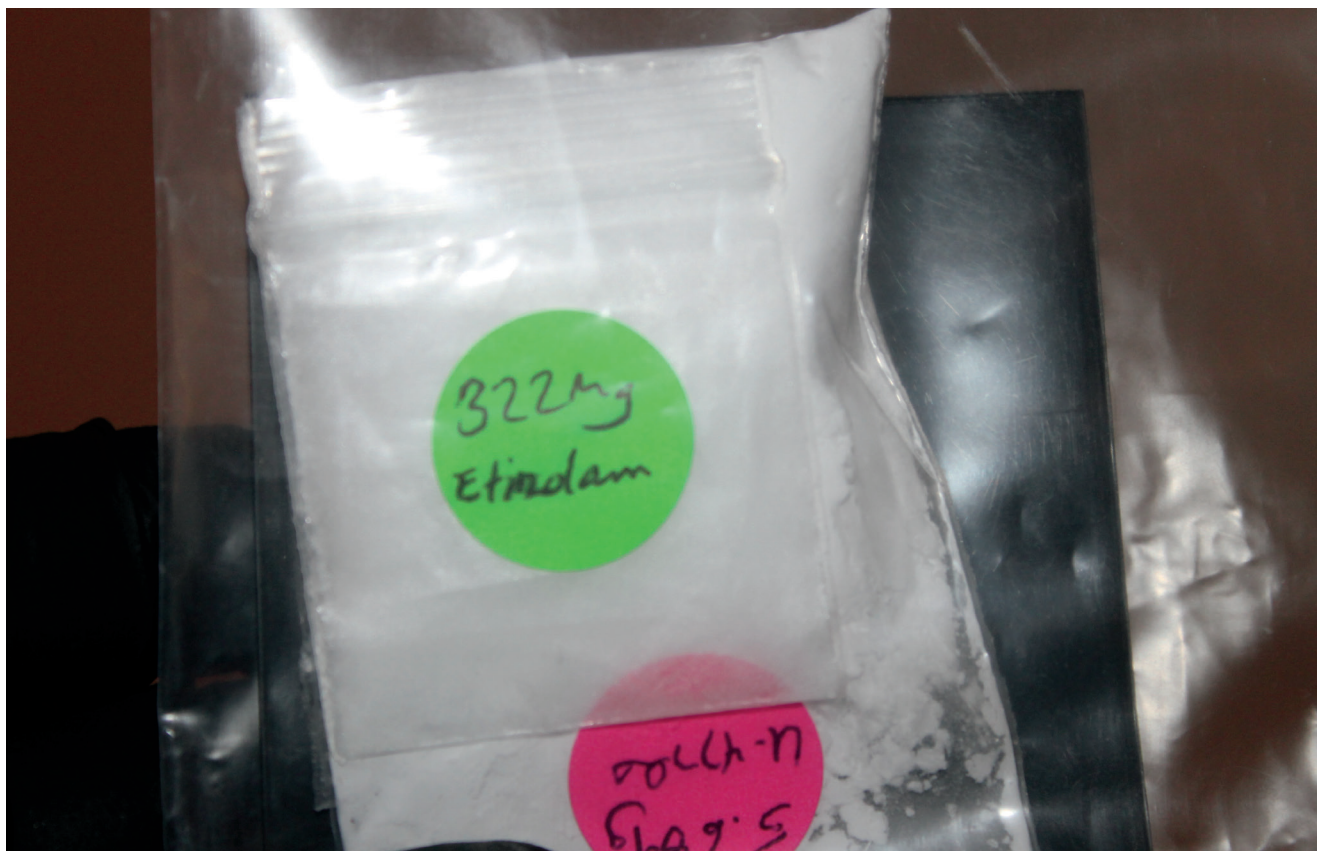


Image 2: Labeled plastic baggies containing etizolam and U-47700 confiscated in Case 2.

Table 1: Demographics, Cause of Death, Manner of Death, and Additional Findings in Case Series

Case	Age	Gender	Case History	Cause of Death	Illicit Opioid	Toxicological Findings	Matrix
1	28	Male	Individual was found dead in bed at home. He was supine with dried white froth on his mouth and nose. His history included report of a “chest cold” with fever and sore throat shortly prior to death. Several plastic baggies labeled as “U-47700”, “etizolam”, “butyrfentanyl”, and “4-2CO-MET” were found in decedent’s room. Drug paraphernalia (e.g., cut straws, crushed white powder, needles, and syringes) were also found near the decedent. Significant autopsy findings included pulmonary edema, hypertensive-type cardiomegaly, and chronic active hepatitis with steatosis. Intravenous injection sites were not identified on the body, and polarizable foreign material was not identified in histologic sections of the lungs.	Acute oxycodone and U-47700 overdose	U-47700 189 ng/mL	Oxycodone 67 ng/mL Dextro/levo methorphan 17 ng/mL	Femoral blood
2	18	Male	Individual was found supine on the bedroom floor dead at home. He had bloody fluid on his nose and cheek. His medical history was significant for celiac disease. Baggies labeled “etizolam” and “U-47700” were found at the scene. Multiple items of drug paraphernalia (e.g., needles, syringes, blotter paper), as well as multiple other bottles of vitamins and packages of magnesium citrate, were found near the decedent. Significant autopsy findings included pulmonary edema, cerebral edema, asthma, and focal subgaleal hemorrhage consistent with a terminal fall. Microscopy was significant for peribronchiolar acute and chronic inflammation with a prominence of eosinophils in the lungs.	U-47700 and etizolam toxicity	U-47700 547 ng/mL	Etizolam - Positive	Femoral blood
3	41	Female	Individual was found supine in bed at home. The body showed no evidence of trauma, no froth in the nose or mouth, and no evidence of dermal punctures. His medical history was significant for back pain and smoking. No medications, drugs, or paraphernalia were found on scene. Significant autopsy findings included hypertensive cardiomegaly and pulmonary emphysema. No dermal punctures were identified at autopsy. Histology was not performed.	Acute combined drug overdose (oxymorphone, buprenorphine, and fentanyl)	Fentanyl 12.1 ng/mL	Oxymorphone 11 ng/mL Delta-9-THC 3.4 ng/mL Delta-9-carboxy-THC 19 ng/mL 11-Hydroxy-delta-9-THC 1 ng/mL Buprenorphine 0.79 ng/mL Norbuprenorphine 2.6 ng/mL	Femoral blood
4	31	Male	Individual was taken to a hospital after being found unresponsive by friends in his apartment. He reportedly ingested alprazolam and snorted oxymorphone and/or heroin prior to being found unresponsive. He remained hospitalized for two days prior to death during which time he was treated for complications of a drug overdose. Significant autopsy findings included diffuse cerebral edema with temporal and cerebellar herniation, small pulmonary embolism with acute subpleural pulmonary infarction, and absence of the heart, liver, and kidneys due to organ donation. Histology was not performed. Antemortem peripheral blood was collected in blue vial, gray vial, lavender vial, and antemortem serum in green and gold vials.	Acute combined drug overdose (alprazolam, hydrocodone, and fentanyl)	Fentanyl 5.8 ng/mL	Naloxone - Positive Alprazolam 44 ng/mL Hydrocodone 19 ng/mL Phentermine 88 ng/mL	Antemortem blood

THC - Tetrahydrocannabinol

Table 1: Continued

5	50	Male	Individual was found unresponsive inside of his burning home. He was transported by emergency medical personnel to a hospital where he was pronounced dead shortly after arrival. No drugs or drug paraphernalia were identified on scene; however, the residence sustained significant damage from the fire, possibly precluding the identification of drugs and/or paraphernalia. His medical history was significant for hypertension, coronary artery disease, and crack and heroin use. Significant autopsy findings included soot in the nose, trachea and bronchi, scattered superficial cutaneous burns on his back, pulmonary edema, and hypertensive cardiomegaly. Histology was not performed. Postmortem blood showed 57% carboxyhemoglobin, indicative of smoke inhalation. Hospital blood was collected in light blue, lavender, and red vials; hospital serum was collected in a green vial.	Smoke inhalation with heroin and furanyl fentanyl toxicity as a contributory cause	Furanyl fentanyl 6.5 ng/mL	Levamisole and warfarin - Positive BZE 1000 ng/mL Morphine 10 ng/mL Delta-9-THC 3.3 ng/mL Delta-9-carboxy-THC 27 ng/mL 11-Hydroxy-delta-9-THC 2.4 ng/mL 6-MAM in vitreous 4.4 ng/mL	Hospital blood
6	43	Male	Individual was transported to a hospital after being found unresponsive at a friend's residence. He was pronounced dead shortly after arrival at the hospital. Syringes were found in the decedent's clothing during examination at the hospital. His medical history was significant for depression, suicidal ideation, and back pain from remote blunt trauma injuries from a motor vehicle collision. Significant gross and histologic findings at autopsy were hypertensive and atherosclerotic cardiovascular disease, pulmonary edema, emphysema, hepatosplenomegaly with hepatic steatosis, interstitial nephritis, chronic respiratory bronchiolitis, and evidence of remote blunt trauma.	Methamphetamine, acetyl fentanyl, furanyl fentanyl, bupropion and mixed benzodiazepine intoxication	Furanyl fentanyl 2.4 ng/mL	Caffeine - Positive Nordiazepam 51 ng/mL Alprazolam 8.0 ng/mL Bupropion 160 ng/mL Hydroxybupropion 730 ng/ml Carbamazepine 0.47 µg/mL Acetyl fentanyl 0.36 ng/mL Amphetamine 110 ng/mL Methamphetamine 3900 ng/mL Risperidone 2.2 ng/mL 9-Hydroxyrisperidone 5 ng/mL Diphenhydramine 130 ng/mL	Femoral blood
7	32	Male	Individual became unresponsive while "snoring" with his head down on a table in a friend's residence. Emergency medical personnel pronounced him dead at the scene. There was no evidence of fluid or froth in the nose or mouth. According to his friend, the decedent appeared "intoxicated" when he stopped breathing. He had no known medical history. Significant findings at autopsy were hypertensive cardiovascular disease, dilated cardiomyopathy, and frothy fluid in the lungs. No dermal puncture sites were identified at autopsy. Histology was not performed.	Furanyl fentanyl intoxication and hypertensive cardiovascular disease	Furanyl fentanyl 7.3 ng/mL	Ethanol 99 mg/dL	Femoral blood
8	44	Male	Individual was found unresponsive in the lobby of an apartment complex. He was transported by emergency medical personnel to a hospital where he was pronounced dead shortly after arrival. A baggie containing white powder was found by hospital personnel in a pocket of the decedent's pants. The baggie was discarded by hospital personnel. Significant gross and histologic autopsy findings were hemorrhagic pulmonary edema, hypertensive cardiomegaly, hypoxic-ischemic changes in the brain, fibromuscular dysplasia of coronary arteries, Hashimoto thyroiditis, and obesity. Lung microscopy showed "birefringent particles with associated fibrosis."	Furanyl fentanyl intoxication and metabolite despropionyl-fentanyl	Furanyl fentanyl 12.4 ng/mL	Naloxone - Positive Delta-9-THC 0.84 ng/mL	Femoral blood

BZE - Benzoylcegonine

6-MAM - 6-Monoacetylmorphine

Table 1: Continued

9	28	Male	Individual found unresponsive in his residence. Emergency medical personnel arrived and attempted resuscitation, but death was pronounced at the scene. Drug paraphernalia found on scene included needle with syringe containing liquid, a shoelace indicated to be a tourniquet, and loose pills found in a vial attached to a key ring. His medical history was significant for intravenous drug use. Significant gross autopsy findings include pulmonary edema and dermal punctures on the forearms. Histologic sections show polarizable, birefringent material in the lungs, liver, and spleen.	Combined despropionyl fentanyl and furanyl fentanyl intoxication	Furanyl fentanyl 2.0 ng/mL	Caffeine and naloxone - Positive Morphine 9.2 ng/mL Oxymorphone 6.4 ng/mL Bupropion 37 ng/mL Hydroxybupropion 480 ng/mL 10-Hydroxycarbamazepine 23 µg/mL Paroxetine 81 ng/mL Delta-9-carboxy-THC 14 ng/mL Morphine in vitreous 9.5 ng/mL 6-MAM in vitreous 1.4 ng/mL	Femoral blood
10	22	Male	Individual was found deceased lying face up in a bed in a motel room. He was last known alive approximately one hour prior to being found, and reportedly snorted "fentanyl" and consumed ethanol at that time. There was no indication of drug paraphernalia at the scene. The decedent's medical history is significant for an accidental "fentanyl" overdose the month prior to his death. There was a report of a recent domestic physical altercation. Significant gross autopsy findings include pulmonary edema and hemoaspiration, abrasions and contusions of the nose, and a laceration on the underside of the chin. Histologic sections show aspirated gastric contents and hemoaspiration.	Acute combined drug overdose (furanyl fentanyl and ethanol)	Furanyl fentanyl 42.9 ng/mL	Ethanol 162 mg/dL Caffeine and naloxone - Positive 7-aminoclonazepam 49 ng/mL Paroxetine 17 ng/mL	Femoral blood
11	62	Male	Individual was found dead lying in the floor of his bedroom at home. He was last known alive, when he was "falling asleep" while trying to eat, approximately three hours prior to being found. Hydrocodone, oxycodone, and other nonopioid medications prescribed for the decedent were found at the scene. Drug paraphernalia were not present. His medical history was significant for hypertension, "cardiac problems", and chronic pain. An autopsy was not performed.	Furanyl fentanyl intoxication with hypertensive cardiovascular disease as a contributory cause	Furanyl fentanyl 3.3 ng/mL	Dihydrocodeine/hydrocodol 5.9 ng/mL Hydrocodone 9.4 ng/mL	Femoral blood

cases, as other findings varied from other opioids as listed previously, stimulants such as methamphetamine, benzodiazepines including etizolam, prescription medications, marijuana, alcohol, and others.

CONCLUSION

Postmortem cases involving NPS, including the novel illicit opioids furanyl fentanyl and U-47700, continue to pose challenges. This case series highlights the successful collaboration between scene investigators, forensic pathologists, and toxicologists in identifying novel illicit opioids in addition to routine toxicological findings, therefore resulting in a comprehensive death investigation. The collaborative nature of these types of investigations will continue to be needed for the successful resolution of NPS type cases as more and more novel illicit opioids appear in death investigations.

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