

U-47700 – Incidence of a Novel Psychoactive Substance in a Series of Medical Examiner Cases in Oakland County, MI

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Abstract

U-47700 is one of many drugs that have been part of a group of compounds called novel psychoactive substances (NPS). U-47700 is a synthetic opioid agonist developed by Upjohn pharmaceuticals but never approved. The Oakland County Medical Examiner's Office in Pontiac, Michigan, began observing this compound in the fall of 2016, primarily in cases with other drugs of abuse and NPS. This communication described 18 drug-related deaths in which U-47700 was detected. Blood U-47700 concentrations ranged from 0.37 to 370 ng/mL (mean 35 and median 4.9 ng/mL). Other opioids were detected in 83% of the cases. Other drugs present in these cases are described as well as the scene investigation. While only one death was likely due directly to U-47700, the cases described here demonstrate how NPS have become an important consideration in evaluating drug-related deaths today.

Keywords: Autopsy, death, investigation, Michigan, opioid, overdose, U-47700

INTRODUCTION

The Oakland County Medical Examiner's (OCME) Office serves Oakland County, Michigan, a Southeast Michigan County with a population of about 1.2 million people. Between 2015 and 2018, the office investigated over 7000 deaths annually with between 1060 and 1100 cases transported to the OCME for inspection or autopsy during this period. Of these, autopsies were performed on an average of 922 cases annually.

The incidence of drug-related deaths continues to increase each year now surpassing motor vehicle accident deaths.^[1] The abuse of opioids has been on the rise throughout the United States earning the name "opioid crisis." In 2016, 426 out of 1102 deaths (38.6%) investigated by the Oakland County (Michigan) Medical Examiner's Office were positive for opiates. In 2015, an estimated 17.7 million people worldwide were users of opioids.^[2] There are many types of opioids including natural products such as morphine and codeine; semi-synthetic opioids such as hydrocodone, oxycodone, and hydromorphone; and synthetic opioids such as fentanyl.^[3] In addition, so-called designer opioids have been increasing on the illicit drug market and have also been linked to the growing opioid crisis in the United States.^[4] Deaths involving the drug fentanyl and its analogs exceeded those involving heroin in 2016.^[5] Between 2009 and 2013,

the number of deaths involving an opiate or opioid increased by 57%, whereas synthetic opioid-related deaths increased by 79%.^[6] Before 2015, fentanyl was the main synthetic opioid detected in casework, but now, fentanyl analogs, as well as nonfentanyl opioid agonists, such as U-47700, have appeared on the recreational market.^[7] The number of deaths related to these synthetic opioids is believed to be underestimated since many laboratories do not test for fentanyl or other related analogs, or their testing procedures may lack the sensitivity needed to detect these compounds.^[4] For example, if immunoassay testing is performed, designer opioids might go undetected due to the limited cross-reactivity of these drugs with immunoassay kits, or due to the cutoff concentrations applied.^[8] Despite these limitations, there has been an estimated 5-fold increase in overdose deaths related to synthetic opioids, excluding methadone, over 3 years from 2013 to 2016.^[9]

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In 2016, U-47700 was ranked the 13th most identified drug by the National Forensic Laboratory Information System.^[10] U-47700 was first developed as an opioid analgesic drug by Upjohn pharmaceuticals in the 1970s.^[11] It was structurally related to AH-7921 which was an experimental opioid agonist developed by the drug company Allen and Hanbury.^[3] Although U-47700 has not been tested on humans, animal testing results demonstrated selective u-opioid receptor agonist activity that was about 7–8 times the potency of morphine.^[12] U-47700 is expected to produce effects that are similar to those of potent opioid agonists, such as euphoria, constipation, sedation, analgesia, itching, and respiratory depression. Users of U-47700 on Internet forums have reported that U-47700 acts similarly to morphine or heroin in that it causes positive symptoms such as euphoria and a general lift in mood, but also negative symptoms like nausea.^[13] The effects of opioids, including the synthetic opioid U-47700, are commonly reversed with the use of naloxone. Naloxone hydrochloride, also known as Narcan, is a drug that can temporarily stop some of the life-threatening effects from opioid overdoses, especially the respiratory depression and unconsciousness that comes during an opioid overdose. More than one dose may be needed of naloxone to reverse some overdoses, and sometimes, naloxone might be inadequate by itself if someone took large quantities of opioids or took potent or long-acting opioids.^[14] On the street, U-47700 is most commonly known as “Pink,” “Pinky,” or “U4” due to its white to light pink color. It has been found in both the powder and tablet forms. This drug is most commonly imported to the United States primarily from laboratories in China and is being sold at roughly \$30 per gram.^[15] U-47700 was not initially scheduled by the Drug Enforcement Administration when cases began to appear, but later became a temporary Schedule 1 substance on November 14, 2016.

METHODS

Postmortem data were obtained from the OCME electronic database, as well as from their paper files for all deaths that involved U-47700 beginning with the first reported death on September 25, 2016. Through 2018, there have been 18 reported U-47700 positive cases at the OCME. These cases were evaluated as to cause and manner of death and other drugs detected in addition to U-47700. Police reports were examined to determine if any type of powder, tablets, or other drug paraphernalia was found at the scene, as well as needle marks for points of entry. Initial toxicology testing was performed at the OCME with comprehensive quantitative postmortem toxicology testing for drugs of abuse and prescription drugs performed by a reference laboratory. U-47700 was quantified by LC-MS/MS Liquid Chromatography/Mass Spectrometry; using methods validated by the reference laboratory.^[3] In two cases, U-47700 was determined qualitatively by GC/MS Gas Chromatography/Mass Spectrometry.

RESULTS AND DISCUSSION

Table 1 describes each of the 18 cases in which U-47700 was

detected. All cases, except 10 and 14, were male. The cause of death in every case was either drug abuse or drug intoxication with the manner of death reported as undetermined. Notably, pulmonary edema was present in all cases except case 7 (which was decomposed and the body discovered about 3 weeks after death). Noncardiogenic pulmonary edema is a common complication of an opioid overdose. It is important to note that as common opioids like heroin can cause pulmonary edema, designer opioids including U-47700 are just as likely to possess this complication. The toxicology results were notable in that combined drug use was present in all 18 cases. Only three cases were positive for naloxone suggesting that many deaths occurred before medical treatment as the use of naloxone was quite common during the study period in general.

U-47700 was quantitated in 16/18 cases ranging from 0.37 to 370 ng/mL with a median concentration of 4.9 ng/mL. In a case report by Strehmel *et al.*, U47700 was measured in cardiac and femoral blood at concentrations of 1250 and 290 ng/mL, respectively, suggesting that U-47700 may undergo postmortem redistribution.^[16] In a report by Fels *et al.*, 26 cases in which all deaths were attributed to a U-47700 intoxication either alone or with other substances, the median U-47700 concentration was 610 ng/mL.^[17] Femoral blood was quantitated in 23/26 of the cases in that study. While the U-47700 concentrations in the OCME population were considerably lower than in other reports, the multiple drug findings were notable. Only one case, case 8, had a considerably high level of U-47700 that was comparable to other published case reports. This is the only case from this report in which it is highly suspected that the cause of death was directly related to an acute overdose of U-47700. All the other cases in this report have relatively low levels of U-47700 and thus their deaths are probably not solely due to these novel psychoactive substances (NPS) alone, but rather to a large number of drugs taken in conjunction with it or mixed in with it.

Table 1 also describes other drugs found by class. Notably, other opiates (including fentanyl) were present in a total of 15 (83.3%) cases. In addition, cocaine (and metabolites), benzodiazepines, and other NPS were each present in 6 cases (33.3%). Cannabinoids were only present in four cases and ethanol in only two (one of which was a liver sample likely due to decomposition). Some additional drugs were observed but did not contribute to the cause of death.

Examination of investigation reports for the case studies indicated recent drug use and paraphernalia in most cases [Table 1]. Case 8, which had the highest U-47700 concentration in this series of cases with 370 ng/mL in femoral blood, had ordered “Xanax” from China. No alprazolam was detected, however the designer benzodiazepine etizolam was present. In the absence of other drugs, this is the one case where U-47700 was suspected to be largely responsible death. Cases 16 and 18 were found dead in the same apartment building 2 days apart. Both cases had low U-47700 concentrations but were acutely positive for 6-acetylmorphine (heroin), fentanyl, and cocaine, suggesting a similar drug source. Both were also positive for cannabinoids.

Table 1: U-47700 positive cases and other toxicology and scene findings

Case	U-47700 (ng/mL)	Matrix	Nx	Other significant findings (ng/mL unless noted)	Scene investigation	OPI	FEN	NPS	COC	BDP	THC	EtOH	Others
1	2.1	FB	-	Carfentanil (0.46), diazepam (63), diphenhydramine (140), furanylfentanyl (0.62), ethanol (39 mg/dL), morphine (26), nordiazepam (78), oxycodone (37)	Unlabeled pill container attached to key ring with peach-colored pills	+		+		+		+	Diphenhydramine
2	+	FB	+	Alprazolam (9.4)	Fresh needle tracks, tether around the left ankle, narcotic paraphernalia						+		
3	7.8	FB	-	Alprazolam (77), carfentanil (0.14), fentanyl (4.0), norfentanyl (0.35), oxycodone (330), THC (2.1), THCC (6.7)	History of mixing pills with heroin per girlfriend (who became Case 14)	+	+	+		+	+		
4	0.37	FB	+	Carfentanil (0.65), morphine (11), fentanyl (7.1), norfentanyl (1.1)	Fresh needle tracks on the right arm, syringe in his hand	+	+	+					
5	28	HB	-	Butyryl/isobutyryl fentanyl (2.3), cocaine (57), BZE (830), diphenhydramine (69), fentanyl (4.6), furanylfentanyl (0.31), morphine (5.5), norfentanyl (0.64)	Spoon and plate with tan-colored substance and lighter at the scene	+	+	+	+				Diphenhydramine
6	45	FB	-	Diphenhydramine (66), fentanyl (7.8), morphine (16), norfentanyl (0.57)	Syringe in his arm with a belt as a tourniquet	+	+						Diphenhydramine
7	+	LIVER	NT	Buprenorphine (63 ng/g), ethanol 50 mg/100g, gabapentin (120 mcg/g), norbuprenorphine (62 ng/g)	Found decomposed with three loose loops of electrical cord around his neck	+						+	Gabapentin
8	370	FB	-	Etizolam (24)	Plastic bag with powder in rolled-up sock; had ordered Xanax from China				+				
9	38	HB	-	6-AM (15), codeine (8.6), fentanyl (12), morphine (270), norfentanyl (2.5)	White powder residue at scene	+	+						
10	27	B	-	6-AM (3.2), codeine (16), fentanyl (15), hydromorphone (4.3), morphine (2200), norfentanyl (2.9), trazodone (230)	Released from rehab last week; no paraphernalia found	+	+						Trazodone

Contd...

Table 1: Contd...

Case	U-47700 (ng/mL)	Matrix	Nx	Other significant findings (ng/mL unless noted)	Scene investigation	OPI	FEN	NPS	COC	BDP	THC	EtOH	Others
11	41	FB	-	BZE (120), fentanyl (0.62), lorazepam (41), norfentanyl (0.29), THC (0.60), THCC (<5.0)	Narcotic paraphernalia including spoon, syringes, folded paper		+		+	+	+		
12	14	FB	-	BZE (1600), cocaine (84), cyclopropylfentanyl (+)	Syringe next to the body			+	+				
13	56	FB	-	Alprazolam (54), fentanyl (33), morphine (9.6), norfentanyl (1.0)	Syringe and spoon with a white substance and a fresh puncture mark	+	+			+			
14	1.3	HB	+	Alprazolam (72), fentanyl (5.6)	Taken to hospital and given naloxone to no avail		+				+		
15	1.0	FB	-	BZE (180), fentanyl (10), morphine (51), norfentanyl (0.57)	Pills in coat, and packages of pills and brown powder	+	+		+				
16	1.1	FB	-	6-AM (1.3), BZE (940), cocaethylene (27), cocaine (290), fentanyl (5.9), morphine (63), 9-hydroxy-risperidone (20), THC 1.0	No paraphernalia at the scene	+	+		+		+		9-hydroxy risperidone
17	1.0	FB	-	Codeine (11), doxepin (210), fentanyl (77), hydromorphone (2.2), lamotrigine (1800), morphine (320), nordoxepin (92), norfentanyl (75)	No paraphernalia at scene	+	+						Lamotrigine, doxepin
18	0.67	FB	-	6-AM (1.2) 7-aminoclonazepam (6.1), BZE (710), cocaine (49), doxepin (89), fentanyl (6.7), morphine (35), nordoxepin (320), norfentanyl (0.90), THC (0.78)	Light color powder residue in folded lottery card, crack pipe	+	+		+		+		Doxepin

Matrix - FB: Femoral blood; HB: Heart blood; B: Postmortem blood; HB: Hospital blood; Nx: Naloxone; NT: Not tested; Findings - 6-AM: 6-acetylmorphine; BZE: Benzoylcegonine; THC: Delta-9-tetrahydrocannabinol; THCC: Delta-9-carboxy tetrahydrocannabinol; OPI: Opiates; FEN: Fentanyl; NPS: Novel psychoactive substances; COC: Cocaine and metabolites; BDP: Benzodiazepines; EtOH: Ethanol

Only six out of the 18 cases had no drug paraphernalia found at the scene. Of the other 12 cases, 6/12 had powder found at the scene ranging from a white color to a brown color. Pills were found at two of the case scenes. For case 1, the pills found were described as being of peach color. As mentioned before, U-47700 has the street name of “Pink,” or “Pinky” due to its light pink color. Six cases had syringes found at the scene and four cases had fresh needle marks. U-47700 can be found in both the tablet and powder forms. It is often mixed with other drugs as seen with the high numbers of co-intoxication with drugs from

various classes. Of the 12 cases that had paraphernalia found at the scene, the powder form seemed to be more superior to the pill form, although the pills could have simply been crushed. The most likely entry route for U-47700 was through parenteral administration through the use of syringes.

CONCLUSION

From the end of 2016 through June 2019, 18 cases presented to the OCME with the designer opiate, U-47700. While only one

case appeared to be an acute use of U-47700, the combination of this drug with other opiates and NPS were significant findings in this case population. As always with NPS, specific drugs come and go and the need to be able to detect and identify new substances can be paramount in death investigations.

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Conflicts of interest

There are no conflicts of interest.

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