Opiates and Opioids:

From the Sumerians to the Fentanyls

Dr. Leo Kadehjian
Palo Alto, California

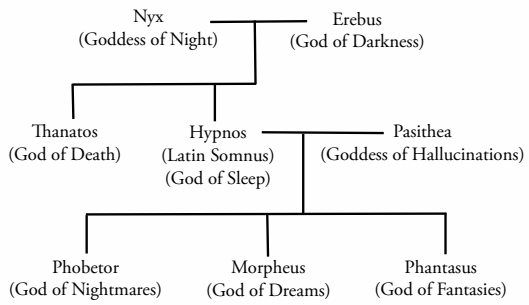
Terminology: "Opiates" or "Opioids"?

- Opiates: Naturally occurring in *Papaver somniferum*
  Morphine, codeine
- Opioids: Act on opiate receptors
  (semi-synthetic, synthetic)
  Oxycodone, hydrocodone, buprenorphine, tramadol, meperidine, methadone, fentanyl, etc.

"Opiates are outranked only by alcohol as humanity's oldest, most widespread, and most persistent drug problem"

Harvard Mental Health Letter, 2004

Ancient Deities Related to Opiates?



Opiates: History

5000 BC	Sumerians "Plant of joy"
400 BC	Pain reliever (Hippocrates, Galen, Dioscorides)
1530	Paracelsus mixes opium with alcohol ("laudanum")
1700s	1st modern anti-drug laws, China, against opium
1803	Morphine isolated ("Morpheus")
1822	De Quincey *Confessions of an English Opium Eater*
1832	Codeine isolated
1839, 56	Opium Wars (Hong Kong ceded to British)

Opiates: History

1853	Hypodermic syringe invented
1861-5	Civil War, 400,000 addicts ("soldier's disease")
1874	Diacetylmorphine synthesized
1875	S.F. ban on "opium houses" (1st US drug law)
1898	Bayer markets Heroin (from "heroisch"), as non-addictive alternative to morphine!!!??? (same year as aspirin)
1906	U.S. Pure Food and Drug Act, labelling requirements
1909	Opium Exclusion Act, no importation International Opium Commission, Shanghai

Opiates: History

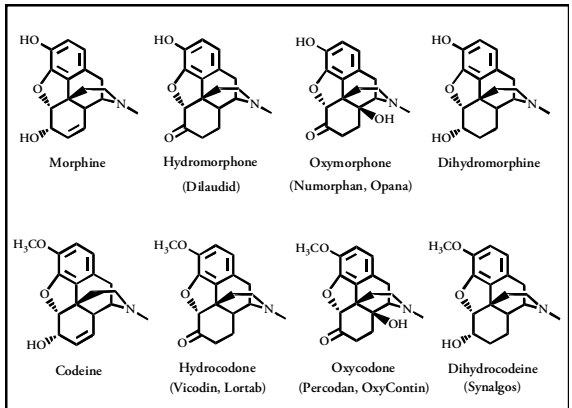
1914	Harrison Narcotic Act, heroin controlled (<10 mg/g)
1923	Morphine structure
1924	Heroin Act, heroin illegal
1937	Methadone synthesized
1938	Meperidine (Demerol) introduced
1950s	Morphine total synthesis
1960s	Methadone maintenenace
1970s	Opiate receptors discovered Enkephalins, endorphins, discovered

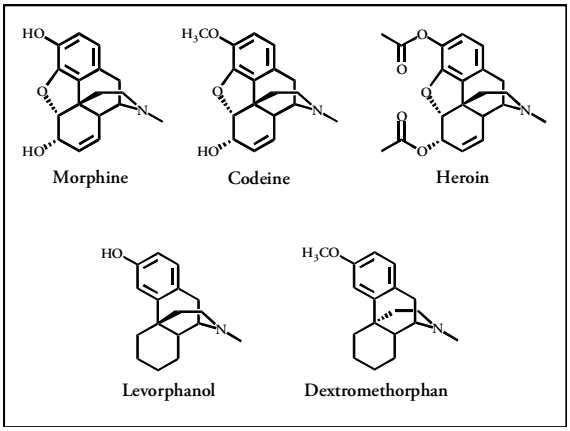
Opiates: History

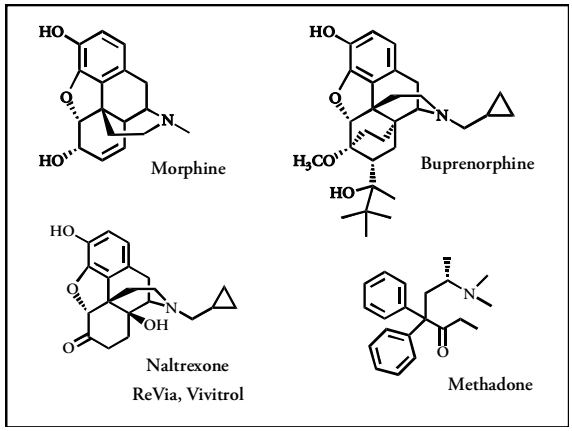
1993	Morphine μ-receptor sequenced, cloned
1990s	Heroin trials: Switzerland, several other countries
2000	Drug Addiction Treatment Act
2002	Buprenorphine approved
2006	ER Naltrexone approved for alcoholism treatment
2010	Abuse-deterrent OxyContin
2010	ER Naltrexone approved for opiate abuse treatment
2014-5	IN, IM Naloxone approved
2015-6	CDC, ASAM Opioid Treatment Guidelines

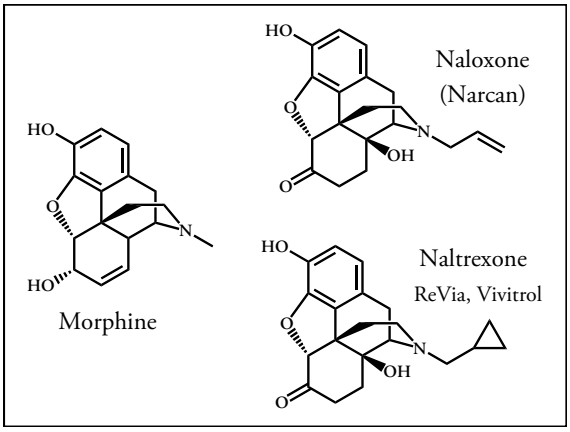
Opioids

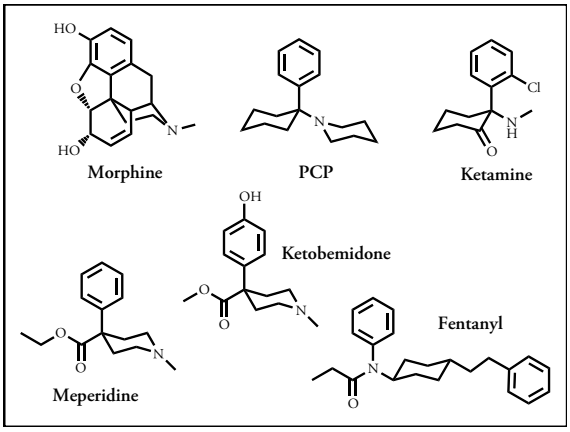
Natural	Semi-synthetic		Synthetic
Morphine	Hydrocodone	Hydromorphone	Methadone
Codeine	Oxycodone	Oxymorphone	Fentanyls
Endorphins	Dihydrocodeine	Dihydromorphine	Meperidine
Mitragynine	Heroin	Levorphanol	Tramadol
	Buprenorphine	Dextromethorphan	Tapentadol
	Naltrexone	Naloxone	Propoxyphene
	Desomorphine ("Krokodil")		W series 1–32
	Etorphine		

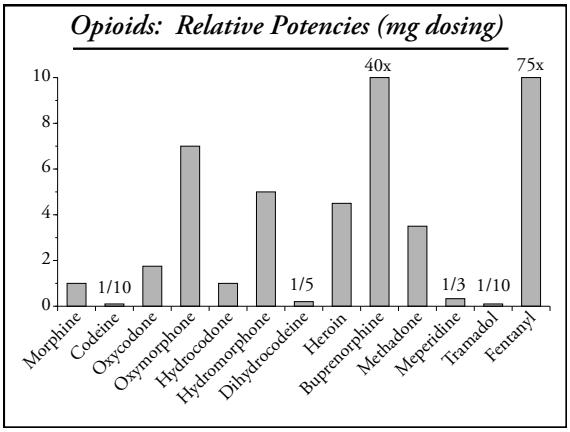


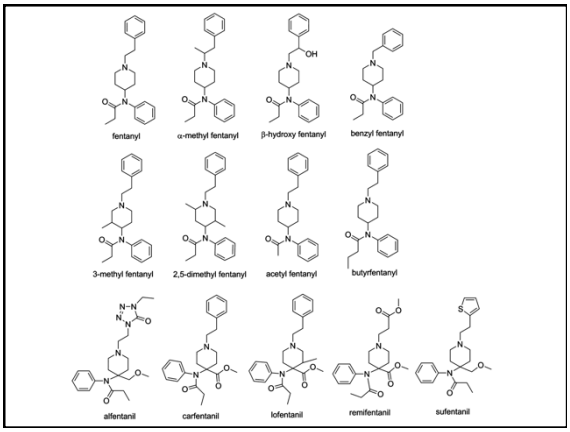












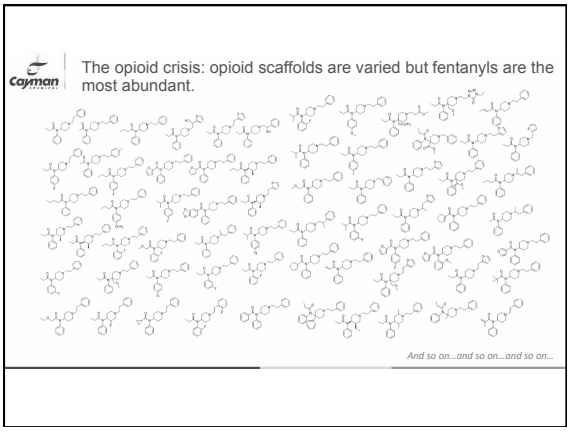
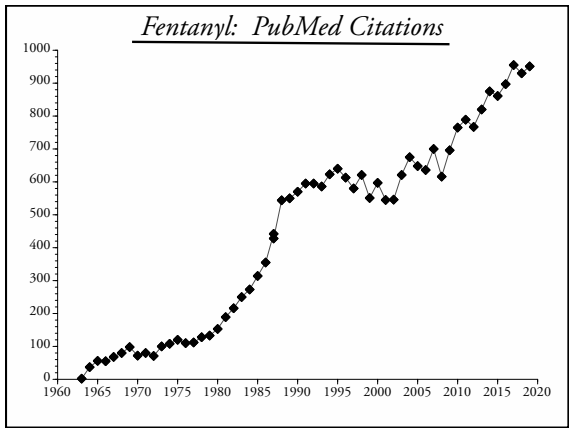
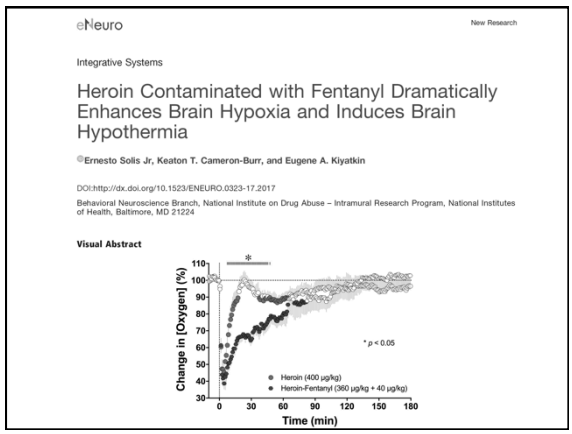


Table 1. Comparison of Fentanyl Analogues in Regards to US DEA Scheduling and Potency[a]

US DEA schedule	compound name	potency ratio to fentanyl	ED_{50} (mg/kg)
Schedule I	acetyl fentanyl	0.29	0.021
	α-methyl fentanyl	1.1	0.0085
	3-methyl fentanyl	0.9−10.5	0.04
	benzyl fentanyl	ND	ND
	β-hydroxy fentanyl	ND	0.0018
	butyryl fentanyl	0.03−0.13	0.220[52]
	lofentanil	>100	ND
Schedule II	alfentanil	0.1−0.2	0.044
	carfentanil	100	0.00041
	remifentanil	2−20	0.0044
	sufentanil	5−10	0.00071
	fentanyl	1	0.0041[53]


Fentanyl: PubMed Citations
1000
900
800
700
600
500
400
300
200
100
0
1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015 2020


The NEW ENGLAND JOURNAL of MEDICINE
Perspective
FEBRUARY 16, 2017
Addressing the Fentanyl Threat to Public Health
Richard G. Frank, Ph.D., and Harold A. Pollack, Ph.D.
Fentanyl, a powerful synthetic opioid, poses an increasing public health threat. Low production costs encourage suppliers to "cut" heroin with the drug, particularly white powder heroin sold in
ed States, recent fatalities have also been attributed to fentanyl in counterfeit Xanax (alprazolam), Norco (acetaminophen–hydrocodone), and other medications.


eNeuro
New Research
Integrative Systems
Heroin Contaminated with Fentanyl Dramatically Enhances Brain Hypoxia and Induces Brain Hypothermia
Ernesto Solis Jr, Keaton T. Cameron-Burr, and Eugene A. Kiyatkin
DOI:http://dx.doi.org/10.1523/ENEURO.0323-17.2017
Behavioral Neuroscience Branch, National Institute on Drug Abuse – Intramural Research Program, National Institutes of Health, Baltimore, MD 21224
Visual Abstract
Change in [Oxygen] (%)
Time (min)
* p < 0.05
Heroin (400 µg/kg)
Heroin-Fentanyl (360 µg/kg + 40 µg/kg)

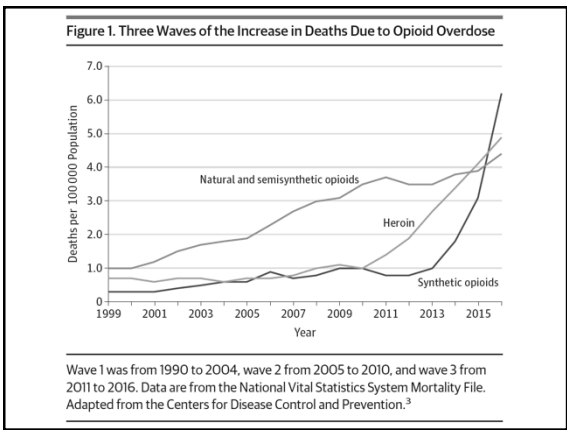


Figure 1. Three Waves of the Increase in Deaths Due to Opioid Overdose
Deaths per 100 000 Population
Natural and semisynthetic opioids
Heroin
Synthetic opioids
Year
Wave 1 was from 1990 to 2004, wave 2 from 2005 to 2010, and wave 3 from 2011 to 2016. Data are from the National Vital Statistics System Mortality File. Adapted from the Centers for Disease Control and Prevention.[3]

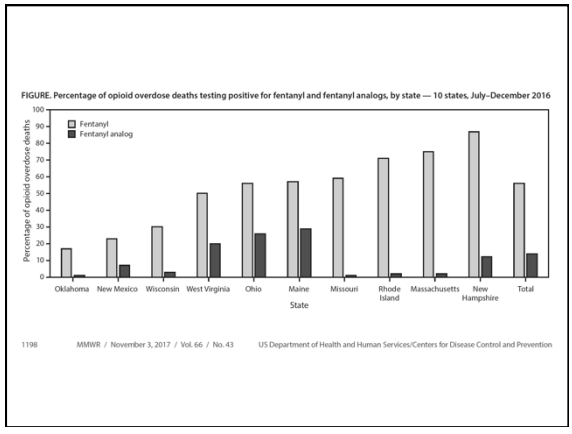
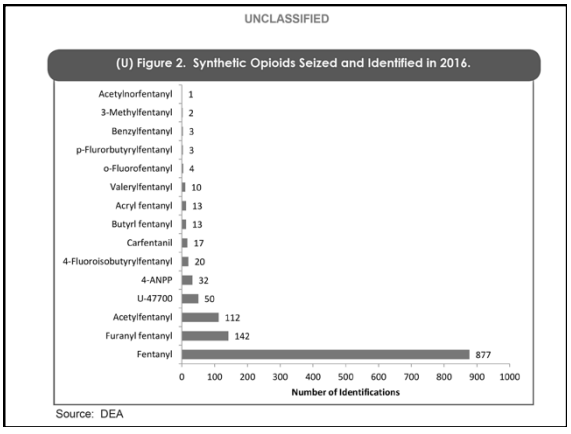
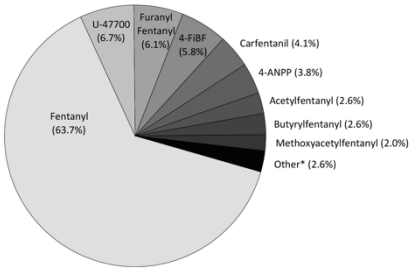


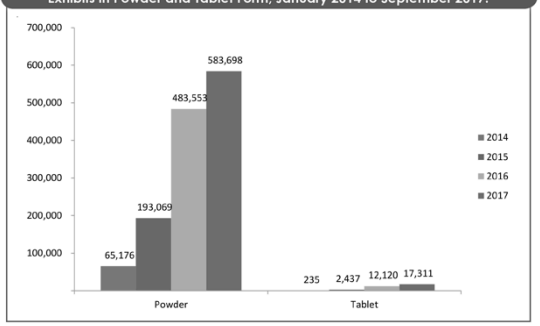
FIGURE. Percentage of opioid overdose deaths testing positive for fentanyl and fentanyl analogs, by state — 10 states, July–December 2016
Fentanyl
Fentanyl analog
Percentage of opioid overdose deaths
Oklahoma
New Mexico
Wisconsin
West Virginia
Ohio
Maine
Missouri
Rhode Island
Massachusetts
New Hampshire
Total
State
1198 MMWR / November 3, 2017 / Vol. 66 / No. 43 US Department of Health and Human Services/Centers for Disease Control and Prevention


UNCLASSIFIED
(U) Figure 2. Synthetic Opioids Seized and Identified in 2016.
Acetylnorfentanyl 1
3-Methylfentanyl 2
Benzylfentanyl 3
p-Flurorbutyrylfentanyl 3
o-Fluorofentanyl 4
Valerylfentanyl 10
Acryl fentanyl 13
Butyrl fentanyl 13
Carfentanil 17
4-Fluoroisobutyrylfentanyl 20
4-ANPP 32
U-47700 50
Acetylfentanyl 112
Furanyl fentanyl 142
Fentanyl 877
Number of Identifications
Source: DEA

Opioids Identified in Drug Evidence Analyzed by the DEA Laboratory System, Third Quarter 2017
(N=344 opioid identifications)



(U) Figure 7. Total Weight of Analyzed Fentanyl and Fentanyl Related Substance Exhibits in Powder and Tablet Form, January 2014 to September 2017.



Source: DEA

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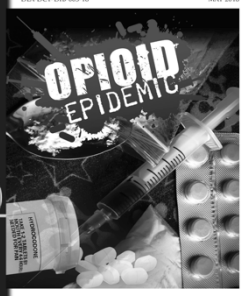
DEA INTELLIGENCE BRIEF

Fentanyl Remains the Most Significant Synthetic Opioid Threat and Poses the Greatest Threat to the Opioid User Market in the United States

DEA-DCT-DIB-003-18 MAY 2018



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ACS Chemical Neuroscience Review

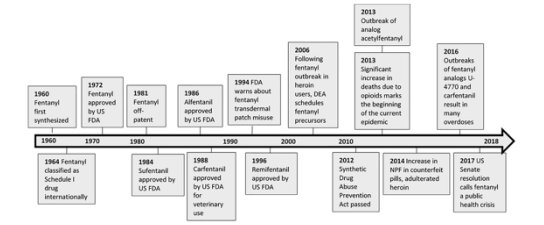


Figure 3. Timeline of select fentanyl events in US history.

DEPARTMENT OF JUSTICE

Drug Enforcement Administration

21 CFR Part 1308

[Docket No. DEA–476]

Schedules of Controlled Substances: Temporary Placement of Fentanyl-Related Substances in Schedule I

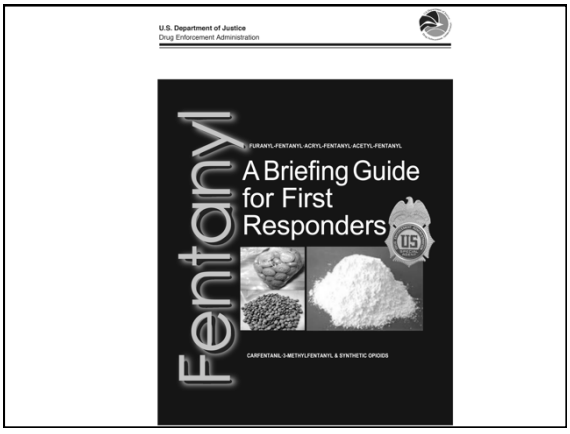
AGENCY: Drug Enforcement Administration, Department of Justice.

ACTION: Temporary amendment; temporary scheduling order.

SUMMARY: The Administrator of the Drug Enforcement Administration is issuing this temporary scheduling order to schedule fentanyl-related substances that are not currently listed in any schedule of the Controlled Substances Act (CSA) and their isomers, esters, ethers, salts and salts of isomers, esters, and ethers in schedule I. This action is

Fentanyl

- Much cheaper than heroin: 1–3 $K/kg vs. 20–40$K/kg
- Mu opiate receptors agonist: MOR1: analgesia, MOR2: respiratory depression, miosis, constipation, euphoria
- Dosing: IV 25–100 µg, patches: 2.5–10 mg deliver 25–100 µg/hr
- ED_{50}: 0.0041 mg/kg = 287 µg/70 kg, only a few mg deadly
  Respiratory depression, chest wall rigidity
- OD death: only a few minutes vs. heroin 30 minutes
- High V_d, very lipophilic, high tissue distribution
- $t_{1/2}$: 2–4 hr (and longer)
- Metabolism: only a few % unchanged in urine, mainly norfentanyl



J. Med. Toxicol. (2017) 13:347–351
DOI 10.1007/s13181-017-0628-2

POSITION STATEMENT

ACMT and AACT Position Statement: Preventing Occupational Fentanyl and Fentanyl Analog Exposure to Emergency Responders

Michael J. Moss[1] · Brandon J. Warrick[2] · Lewis S. Nelson[3] · Charles A. McKay[4] · Pierre-André Dubé[5] · Sophie Gosselin[6] · Robert B. Palmer[7] · Andrew I. Stolbach[8]

OP-ED CONTRIBUTORS

Opioid Hysteria Comes to Massachusetts Courts

By Jeremy Samuel Faust and Edward W. Boyer

Jan. 23, 2018

This month, Massachusetts became the first state to ban fentanyl and carfentanil from being brought into courthouses as exhibits, out of concern that these substances are simply too dangerous to be in public places. The policy is based in part on the idea that even minuscule amounts of skin exposure to these drugs can be life-threatening. This is patently false — and we fear that it will worsen what is already a public health crisis.

When used properly, fentanyl and carfentanil are therapeutic.

When they are used improperly, they can ruin lives and kill.

And when touched by human hands in powder or liquid form, nothing happens.

J. Faust and E. Boyer, Harvard Medical School, Brigham and Women's Hospital, New York Times, 1/23/18.

Fentanyl and its analogs are potent opioid receptor agonists, but the risk of clinically significant exposure to emergency responders is extremely low. To date, we have not seen reports of emergency responders developing signs or symptoms consistent with opioid toxicity from incidental contact with opioids. Incidental dermal absorption is unlikely to cause opioid toxicity.

The New York Times

Fear, Loathing and Fentanyl Exposure

It's almost impossible to ingest opioids by accident, but misinformation has triggered a panic about the risks.

By The Editorial Board

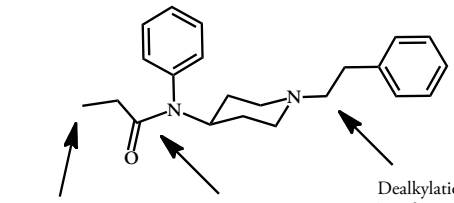
The editorial board represents the opinions of the board, its editor and the publisher. It is separate from the newsroom and the Op-Ed section.

April 4, 2019

As baseless public health scares go, the one about police officers and nurses purportedly overdosing from passive fentanyl exposure should have been easy to dispel. Emergency workers across the country have reported dozens of such incidents in recent years, but their symptoms are often inconsistent with opioid poisoning. In some cases, officers have administered the overdose-reversal drug Narcan to themselves — a feat that would be impossible in the midst of an actual overdose.

In 2017, the nation's two leading toxicological societies published a joint statement explaining that for emergency medical workers, the risk of accidental opioid ingestion is "extremely low." Gloves almost always provide enough protection; masks are necessary only in exceptional cases.

Fentanyl Metabolism



Hydroxylation
Carboxylation

Despropionyl fentanyl
(4-ANPP)

Dealkylation
(Norfentanyl)
(major)

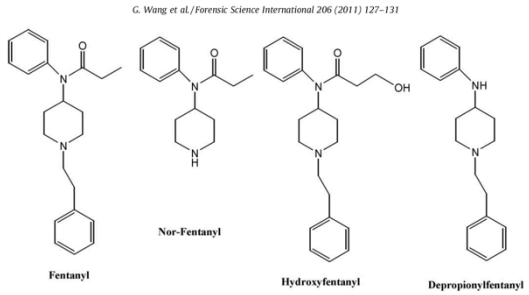


Fig. 1. Chemical structure of fentanyl and its metabolites.

Urine Opioid Concentrations in 184,049 Pain Patients

	Mean	Median	Range
Morphine	29,612 ng/mL	9,600	50 – 1,995,940
Codeine	4,752	828	50 – 233,036
Hydrocodone	2,564	860	50 – 477,876
Hydromorphone	836	240	50 – 204,633
Oxymorphone	5,760	1,299	50 – 1,512,220
Oxycodone	11,207	2,124	50 – 5,947,380
Buprenorphine	313	75	10 – 58,691
Norbuprenorphine	640	279	20 – 13,615
6-Acetylmorphine	1,109	276	10 – 24,069

A. Pesce et al., 2012

Urine Opioid Concentrations in 184,049 Pain Patients

	Mean	Median	Range
Fentanyl	109 ng/mL	36	2 – 33,051
Norfentanyl	627	237	8 – 47,355
Methadone	5,265	2,409	100 – 260,433
EDDP	7,872	4,117	100 – 251,835
Meperidine	34,322	13,533	50 – 616,862
Normeperidine	1,456	339	50 – 276,993
Propoxyphene	1,919	584	100 – 178,006
Norpropoxyphene	5,254	2,027	100 – 167,037
Tapentadol	11,557	6,870	52 – 492,895
Tramadol	19,288	8,191	100 – 601,928

A. Pesce et al., 2012

Journal of Analytical Toxicology, Vol. 28, September 2004

Urine Concentrations of Fentanyl and Norfentanyl During Application of Duragesic® Transdermal Patches

Alphonse Poklis*
Department of Pathology, Virginia Commonwealth University School of Medicine, Richmond, Virginia 23298-0165

Ronald Backer
Ameritox Laboratory, 9930 West Highway 80, Midland, Texas 79706

Table I. Urine Concentrations of Fentanyl and Norfentanyl Following the Application of Duragesic Transdermal Patch

	Duragesic Patch, Dose of Fentanyl			
	25 µg/h	50 µg/h	75 µg/h	100 µg/h
All urine specimens				
Number of specimens	142	184	85	135
Fentanyl mean (ng/mL)	47	74	107	100
Range (ng/mL)	0–983	0–589	0–1280	0–1080
Norfentanyl mean (ng/mL)	175	257	328	373
Range (ng/mL)	0–980	0–2200	0–5630	0–5730
90% of urine specimens				
Number of specimens	128	166	77	121
Fentanyl mean (ng/mL)	32	58	95	79
Range (ng/mL)	0–167	0–250	4–444	0–350
Norfentanyl mean (ng/mL)	173	251	285	327
Range (ng/mL)	0–980	0–860	4–1330	0–1670

Journal of Analytical Toxicology, 2016;40:595–600
doi: 10.1093/jat/bkw067
Advance Access Publication Date: 11 July 2016
Article

OXFORD

Article

Fentanyl–Norfentanyl Concentrations During Transdermal Patch Application: LC–MS-MS Urine Analysis

Oneka T. Cummings[1,*], Jeffrey R. Enders[1], Gregory L. McIntire[1], R. Backer[1], and A. Poklis[2]

[1]Ameritox, Ltd., 486 Gallimore Dairy Road, Greensboro, NC 27409, USA, and [2]Department of Pathology, Virginia Commonwealth University, Richmond, VA 23298, USA

Table I. Data from Fentanyl and Norfentanyl LC–MS-MS analysis

Dose (µg/h)	Number of specimens		Mean concentration (ng/mL)				Max concentration (ng/mL)			
			Fentanyl		Norfentanyl		Fentanyl		Norfentanyl	
	Current	P&B initial[a]	Current	P&B initial[a]	Current	P&B initial[a]	Current	P&B initial[a]	Current	P&B initial[a]
12	3,757	N/A	32	N/A	176	N/A	1,929	N/A	2,515	N/A
25	17,322	142	43	47	221	175	1,971	983	2,502	980
50	22,039	184	74	74	388	257	1,940	589	2,499	2,200
75	16,742	85	106	107	543	328	2,098	1,280	2,500	5,630
100	17,158	135	137	100	695	373	2,000	1,080	2,499	5,730
Total	77,018	546								

The minimum concentrations for both Fentanyl and norfentanyl in this study were observed as being <LOQ (2 and 10 ng/mL, respectively).
[a]The results shown here are taken from the initial work published by Poklis and Backer (3), the minimum concentrations for fentanyl and norfentanyl for all dosages were reported as 0 ng/mL.

Table 3
Cross-reactivity with fentanyl metabolites.

Analytes	Analyte concentration (ng/mL)	Fentanyl concentration (ng/mL)	Cross-reactivity (%)
Despropionyl fentanyl	25	2	8%
Norfentanyl	500	<1	Not detected

Cross-reactivity

Norfentanyl (Major Metabolite)

Compound	Concentration Tested (ng/mL)	Percent Cross-reactivity (%)
Norfentanyl (Major Metabolite)	2.5	10
	300	0.33

Other Metabolites and Structural Analogs of Fentanyl

Compound	Lowest Concentration Tested That Produced a Response Approximately Equivalent to the Cutoff (ng/mL)	Percent Cross-reactivity (%)
Acetyl fentanyl	1.20	83.33
Acrylfentanyl	1.20	83.33
ω-1-Hydroxyfentanyl	1.20	83.33
Isobutyryl fentanyl	1.50	66.67
Ocfentanil	1.50	66.67
Butyryl fentanyl	1.60	62.50
Furanyl fentanyl	1.75	57.14
Valeryl fentanyl	2.50	40.00
β-Hydroxyfentanyl	2.75	36.36
(±) β-hydroxythiofentanyl	2.80	35.71
4-Fluoro-isobutyryl fentanyl	3.00	33.33
Para-fluorobutyryl fentanyl (p-FBF)	3.00	33.33
Para-fluoro fentanyl	3.00	33.33
(±)-3-cis-methyl fentanyl	5.00	20.00
Despropionyl fentanyl (4-ANPP)	75.00	1.33
Carfentanil	500	0.20
Sufentanil	625	0.16
Norcarfentanil	5,000	<0.02
Acetyl norfentanyl	10,000	0.01
Remifentanil	10,000	<0.01
Alfentanil	100,000	<0.001

- **OriginalInvestigation | PublicHealth**

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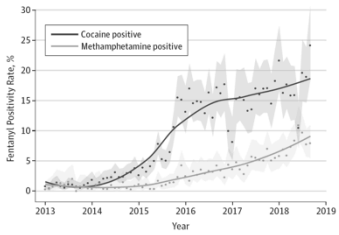
Original Investigation | Public Health

Rate of Fentanyl Positivity Among Urine Drug Test Results Positive for Cocaine or Methamphetamine

Leah LaRue, PharmD, PMP; Robert K. Twillman, PhD; Eric Dawson, PharmD; Penn Whitley, BA; Melissa A. Frasco, PhD; Angela Huskey, PharmD, CPE; Maria G. Guevara, PharmD, CPE

Huskey, PharmD, CPE; Maria G. Guevara, PharmD, CPE

Figure. Nonprescribed Fentanyl Positivity Among Urine Drug Test Results Positive for Cocaine or Methamphetamine



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Evaluation of a lateral flow immunoassay for the detection of the synthetic opioid fentanyl

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Commentary

Fentanyl self-testing outside supervised injection settings to prevent opioid overdose: Do we know enough to promote it?

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ABSTRACT

Since 2013, North America has experienced a sharp increase in unintentional fatal overdoses: fentanyl, and its analogues, are believed to be primarily responsible. Currently, the most practical means for people who use drugs (PWUD) to avoid or mitigate risk of fentanyl-related overdose is to use drugs in the presence of someone who is in possession of, and experienced using, naloxone. Self-test strips which detect fentanyl, and some of its analogues, have been developed for off-label use allowing PWUD to test their drugs prior to consumption. We review the evidence on the off-label sensitivity and specificity of fentanyl test strips, and query whether the accuracy of fentanyl test strips might be mediated according to situated practices of use. We draw attention to the weak research evidence informing the use of fentanyl self-testing strips.