Acūtis Diagnostics

The Synthetics:

Designer Drugs on the Horizon

July 18th, 2019

Featuring Daniela Zaborskis, PhD
and Mumtaz Akhtar, MS

Daniela Zaborskis, PhD

Director of Operations and Senior Scientist, Acutis Diagnostics

Specialized in toxicology diagnostics for over 6 years

Former Teaching Fellow at St. John's University

Mumtaz Akhtar, MS

Senior Research Scientist, Acutis Diagnostics

PhD candidate in toxicology at St. John's University

Disclosures

- Daniela Zaborskis, PhD
  - Affiliation: Acutis Diagnostics
  - Role: Team member
- Mumtaz Akhtar, MS
  - Affiliation: Acutis Diagnostics
  - Role: Team member

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Learning Objectives

- Describe the neuropharmacology and pharmacokinetics of synthetic cannabinoids and fentanyl analogs' addictive potential.
- Identify differences between various synthetic cannabinoids and fentanyl analog products.
- Review the statistics and prevalence of synthetic cannabinoids and fentanyl analogs amongst commonly abused substances
- Review the current state of detection methodologies to detect synthetic cannabinoids and fentanyl analogs.
- Review harm reduction technologies and overdose treatments for these agents.

Pre-Test Questions

According to National Forensic Laboratory Information System, which synthetic cannabinoid was highly reported in 2018 in the United States?

A. XLR-11
B. FUB-AMB
C. 5F-ADB
D. AB-CHMINACA
E. JHW-018

Pre-Test Questions

Which drug is ranked number one for overdose fatalities in the United States?

A . Oxycodone

B . Heroin

C . Cocaine

D . Fentanyl

E . All of the above

Pre-Test Questions

Which of the followings are true regarding fentanyl analogs?

A. In 2017 alone, 28,400 overdose deaths were related to fentanyl, fentanyl analogs and other novel synthetic opioids

B. Fentanyl, its analogs and novel synthetic opioids can be legally prescribed by clinicians with a proper DEA license

C. Pharmacologically, fentanyl, its analogs, and novel synthetic opioids are equally dangerous to most other opioids

D. Naloxone dose use to reverse heroin overdose will also reverse fentanyl and its analogs' toxicity

E. All of the above

Acūtis
Diagnostics

Synthetic Cannabinoids

Daniela Zaborskis, PhD

Synthetic Cannabinoids

- What are they? Naming conventions
- Legal status
- Statistics
- Categories
- Pharmacology and toxicology – drug testing challenges
- Synthetic cannabinoids in the news

What are synthetic cannabinoids?

- *NOT* marijuana
- Often called “synthetic marijuana” or “fake weed”
- Individual or mixtures of different compounds
- Sprayed on psychoactively inert pulverized plant material of unknown content
- Resembles potpourri or incense – “Spice”

What are synthetic cannabinoids?

- Large family of chemically unrelated compounds – functionally similar to delta-9-tetrahydrocannabinol (THC)
- Produced by “street chemists”
- Marketed as safe, legal alternative
- New Psychoactive Substances (NPS)

What are synthetic cannabinoids?

https://www.oasas.ny.gov/AdMed/drugs/Synthetics.cfm

Naming conventions

- Named after the scientist who first synthesized them
- Institution of company where they originated
- JWH – John W. Huffman
- AM – Alexandros Makiyannis
- Brand names – K2, Spice, Black Mamba, Bombay Blue

^ "Synthetic cannabinoids in Europe | www.emcdda.europa.eu". *www.emcdda.europa.eu*.

Legal status

- Individual states
- David Mitchell Rozga Act
- Synthetic Drug Abuse Prevention Act of 2012

^ Vashi, Sonam (September 26, 2012). "K2 Trend Not Slowing Down".

Statistics

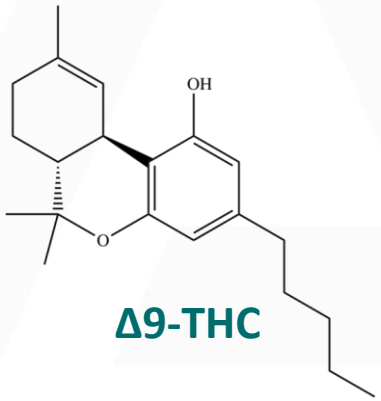
National Forensic Laboratory Information System:

- 2010 – (JWH-018, JWH-250, JWH-073) most common synthetic cannabinoids reported
- 2013 to 2015 – (XLR-11, AB-FUBINACA, AB-CHIMINACA)
- Mid-year 2018 – (5F-ADB, FUB-AMB, ADB-FUBINACA)

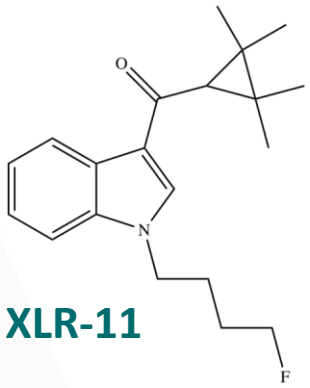
https://www.nflis.deadiversion.usdoj.gov/DesktopModules/ReportDownloads/Reports/NFLIS-SR-SynthCannabinoidCathinone.pdf

Categories

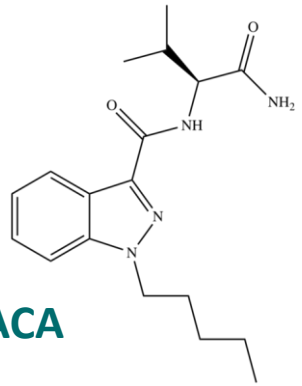
- Classical cannabinoids, non-classical cannabinoids, hybrid, aminoalkylindoles, eicosanoids
- Although not direct THC analogs, share many features
  - Lipid-soluble, non-polar, small molecules, volatile



Δ9-THC



XLR-11



AB-PINACA

Pharmacology

- Cannabis cannabinoid
  - Delta-9-tetrahydrocannabinol (THC)
  - Partial agonist at the CB1 receptor
- Synthetic cannabinoids
  - Full or partial CB1 agonists
  - More potent and efficacious CB1 agonists – may have a longer half-life → greater cannabinomimetic toxicity
- Variability in product composition – wide concentration ranges

Pharmacokinetics and pharmacodynamics

- CB 1 Receptors
  - Most abundant GPCRs expressed in the brain
  - Modulate GABA and glutamate neurotransmitters
- CB 2 Receptors
  - Highly expressed on marginal zone of spleen, tonsils and immune cells
  - Synthetic cannabinoids may affect immune system

Toxicology – acute effects

- Human data concerning induction and duration of adverse effects is limited
- Dynamic, unpredictable nature prevents consistent, quality case reporting

Toxicology – psychoactive effects

- Psychoactive effects
  - Pleasant, desirable euphoria
  - Anxiety, psychosis, alterations to cognitive abilities
- Central effects
  - Seizures, agitation, irritability, memory changes, sedation, confusion

Toxicology – physical effects

- Clinical case reports
  - “Happy Tiger Incense” – JWH-018, JWH-08, JWH-250 and AM-2201→ Generalized convulsions
  - “Smoke” “Spice Gold” → sedation or agitation, hot flashes, burning eyes and xerostomia
  - “Banana Cream Nuke” → tremors and palpitation
- Cardiovascular effects
  - Tachycardia, tachyarrhythmia, cardiotoxicity, chest pain
- Gastrointestinal effects
  - Nausea, vomiting
- Other effects
  - Somnolence, dilated pupils, emesis, appetite changes, tolerance, withdrawal and drug dependence

Toxicology – long-term effects

- No information about the chronic use and toxicity of synthetic cannabinoids
- Speculations based on long-term effects of heavy marijuana use
  - ↑ risk of psychosis
  - New-onset psychosis in otherwise healthy men
    - Auditory and visual hallucinations, paranoid delusions
    - Thought-blocking, disorganized speech
    - Anxiety and insomnia, stupor and suicidal ideation

Toxicology – user profile

- Male adolescents
- 3 main categories based on previous drug use
  - Marijuana smokers
  - Occasional drug users seeking to avoid legal complications
  - Drug-naïve, curious experimenters

Toxicology – Treatment

- No specific antidote
- Activated charcoal – not useful
- Non-psychiatric symptoms – self-limited, resolve with supportive treatment
- Unpleasant psychological effects – supportive treatment
- Withdrawal is not life-threatening
- Significant number – critical care admission

Drug testing challenges

- Screens are unable to detect all designer drugs
- Testing is expanding
- Producers are remarkably flexible in altering psychoactive components to evade regulation and detection
  - Modify functional groups, change substitutions, alter moieties

Synthetic cannabinoids in the news

- Synthetic cannabinoids have been implicated in outbreaks of serious hemorrhagic problems
  - Addition of long-acting anticoagulant rodenticides (LAARs)
- Multistate (Illinois, Indiana, Maryland, Missouri, and Wisconsin) outbreak of hemorrhagic sequelae associated with synthetic cannabinoid use
- Brodifacoum found in all patients

Synthetic cannabinoids in the news

- Brodifacoum is a superwarfarin
  - Ready to use rodent baits
- High oral toxicity, high lipophilicity, accumulates in the liver
  - Hematuria, gingival bleeding, epistaxis, GI bleeding, spontaneous ecchymoses
  - Acute treatment – rapid supplementation of factors through infusion
  - Long term therapy – high-dose vitamin K given the long half-life of LAARs

Synthetic cannabinoids in the news

The New York Times

Overdoses From 'Dangerous Batch' of K2 Grows to 56 in Brooklyn

Authorities are warning that an especially toxic batch of the synthetic drug K2 has been circulating in Brooklyn. At least 56 people have overdosed in recent days, including this man being attended to by emergency medical workers on Sunday in Bushwick. Michelle V. Agins/The New York Times

https://www.nytimes.com/2018/05/22/nyregion/brooklyn-synthetic-marijuana-overdose.html

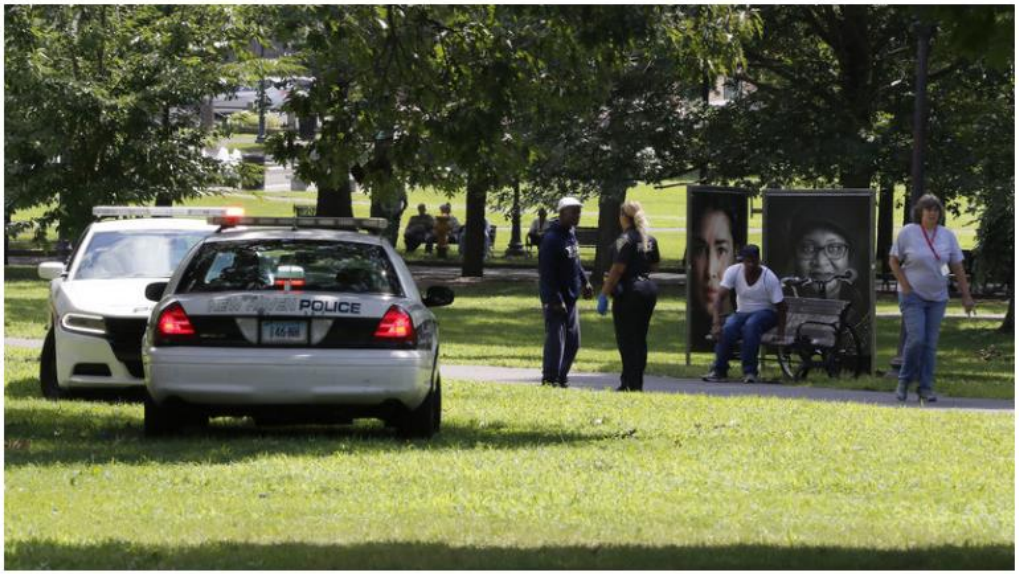
Synthetic cannabinoids in the news

NATIONAL

Dozens Overdose In Connecticut Park On Tainted Synthetic Marijuana

August 16, 2018 · 3:44 AM ET

SCOTT NEUMAN



A police officer speaks to a man on New Haven Green, where more than 70 people fell ill from suspected drug overdoses on Wednesday in New Haven, Conn.

Bill Sikes/AP

https://www.npr.org/2018/08/16/639133355/dozens-overdose-in-connecticut-park-on-tainted-synthetic-marijuana

Acūtis Diagnostics

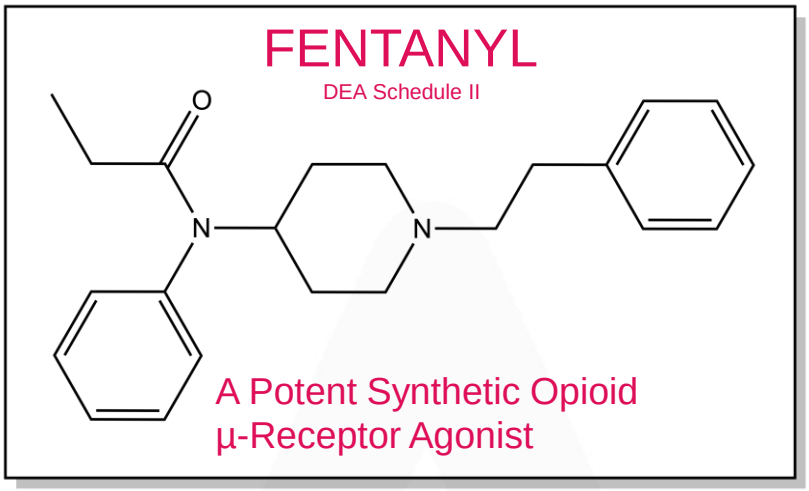
Fentanyl and Fentanyl Analogs

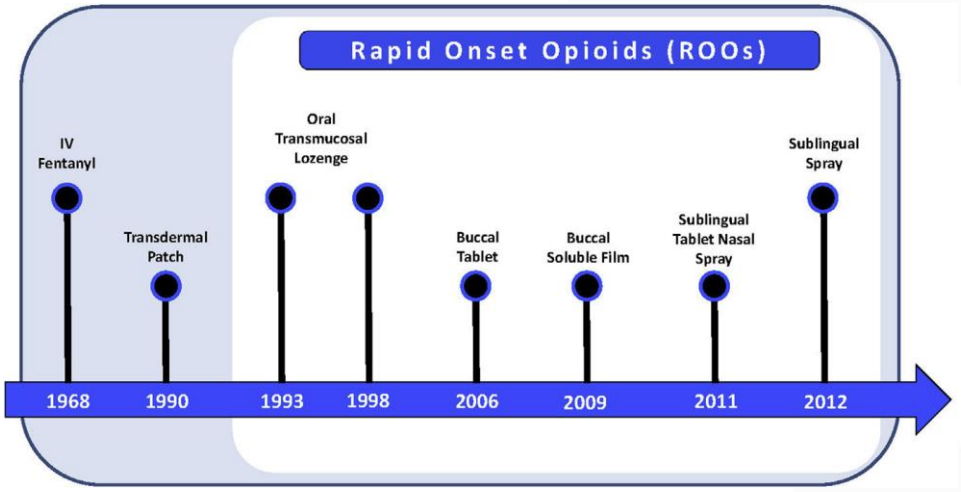
Mumtaz Akhtar, MS

Fentanyl and its analogs

- What are they?
- Legal status
- Neuropharmacology
- Brain disease model of addiction
- The problem?
- Statistics
- Street names, means of use and intentional use
- Current state of drug testing and challenges
- Harm reduction technologies and overdose treatment

What is fentanyl?





Stanley, Theodore. The Fentanyl Story. The Journal of Pain, Vol 15, No 12 (December), 2014: pp 1215-1226

Use: Labeled Indications

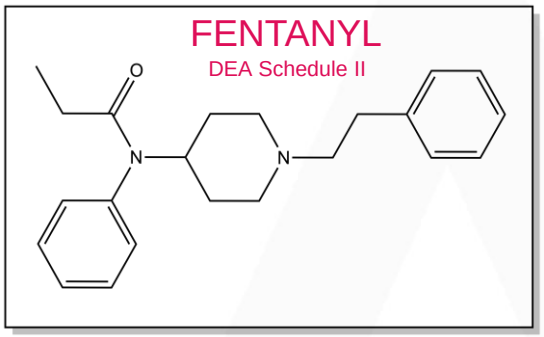
1. Injection: Surgery
2. Transdermal Device: Post-operative acute pain
3. Transdermal Patch: Chronic pain
4. Transmucosal lozenge, buccal tablet and film, intranasal and sublingual spray, and sublingual tablet: Cancer breakthrough pain

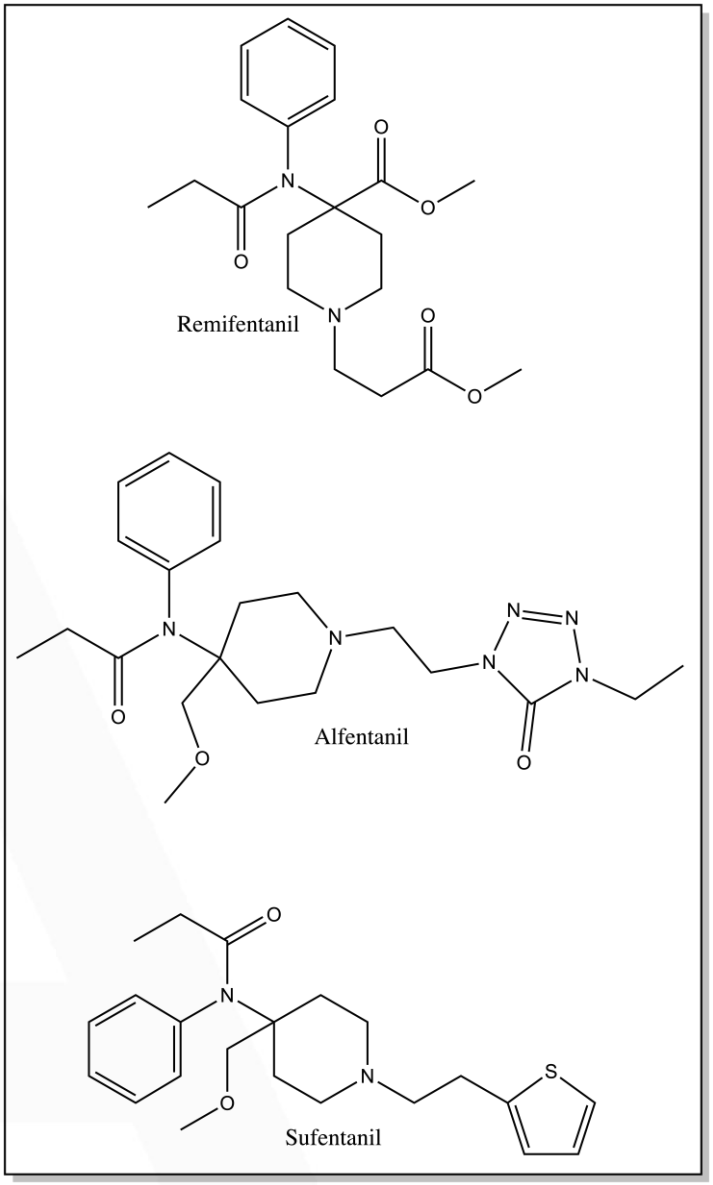
Brand Names: US

- Abstral
- Actiq
- Duragesic
- Fentora
- Ionsys
- Lazanda
- Onsolis
- Sublimaze
- Subsys

Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13e > Opioids, Analgesia, and Pain Management

Legal status: fentanyl congeners – human use





Remifentanil

- Anesthesia: General/ postoperative anesthesia in adults

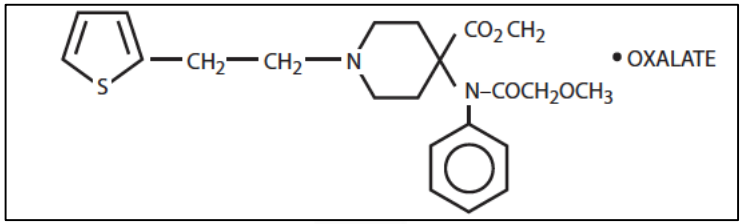
Alfentanil

- Anesthesia: General surgery
- Analgesia: Analgesic adjunct for the maintenance of anesthesia with barbiturate/nitrous oxide/ oxygen

Sufentanil

- Acute Pain Management (Tab. not for home)
- Epidural Anesthesia (Inj.)
- Surgical Anesthesia (Inj.)
- DEA Schedule II

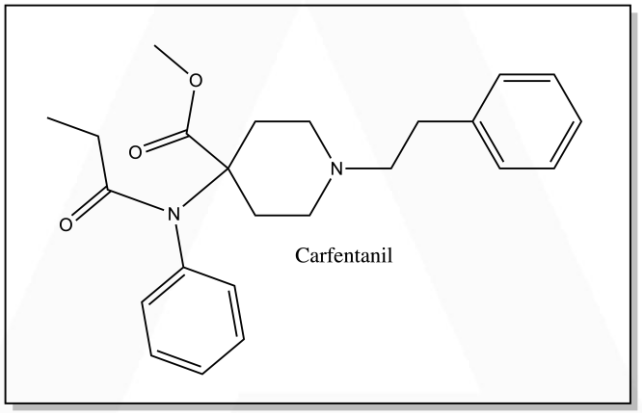
Legal Status: fentanyl congeners – not for use in humans



Thiafentanil (Thianil®)

- Not for use in humans
- Immobilization of captive minor species hoof stock
- 10 mg/mL Injectable
- DEA Schedule II

Wildlife Pharmaceuticals, Inc.
1230 W. Ash Street, Suite D, Windsor, CO 80550



Carfentanil (Wildnil®)

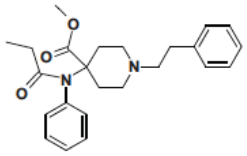
- Not for use in humans
- Intramuscular tranquilizers for large animals
- 3 mg/mL
- Research: Radiolabeled-[^{11}C]-carfentanil to map μ-receptors by positron emission topography
- DEA Schedule II

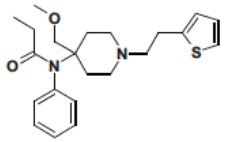
Leen, Jessica, and Juurlink David. 2019. Carfentanil: a narrative review of its pharmacology and public health concerns. Can J Anesth/J Can Anesth. doi.org/10.1007/s12630-019-01294-y

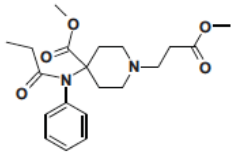
ChemDraw 13.0

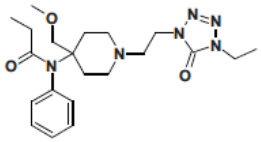
Fentanyl analogs: legal status

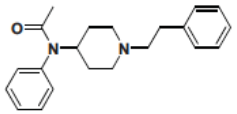
Schedule I

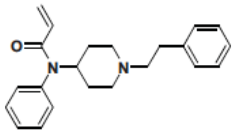

Carfentanil

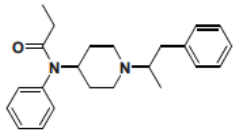

Sufentanil

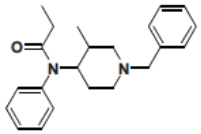

Remifentanil

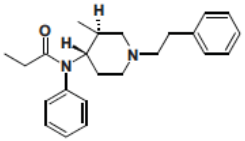

Alfentanil

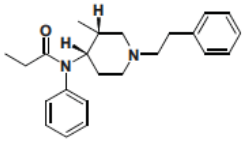

Acetylfentanyl

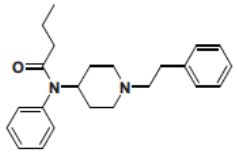

Acryloylfentanyl

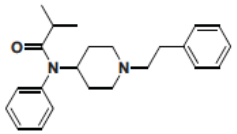

α-Methylfentanyl

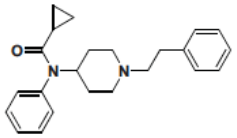

Isofentanyl

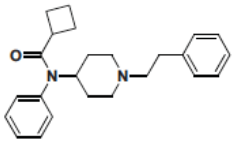

(+)-*Trans*-3-methylfentanyl (3S,4S-configuration)*

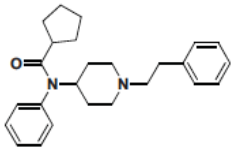

(+)-*Cis*-3-methylfentanyl (3R,4S-configuration)*

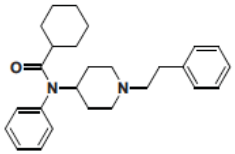

Butyrfentanyl

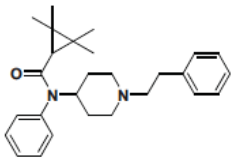

Isobutyrfentanyl

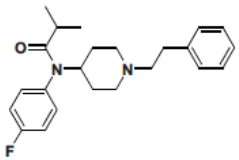

Cyclopropylfentanyl

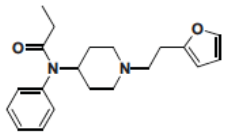

Cyclobutylfentanyl

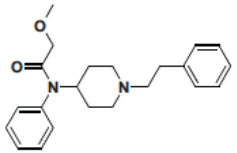

Cyclopentylfentanyl

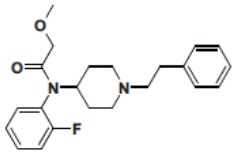

Cyclohexylfentanyl

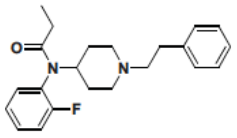

2,2,3,3-Tetramethyl-cyclopropylfentanyl

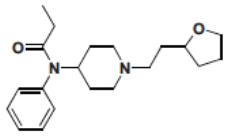

4-Fluoroisobutyr-fentanyl

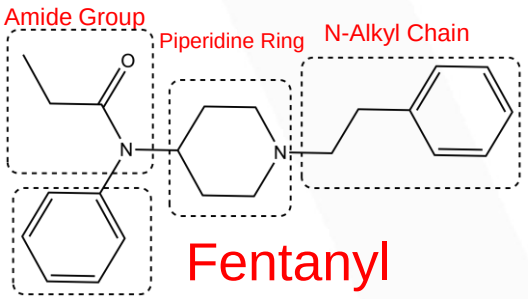

Furanylfentanyl


Methoxyacetylfentanyl


Ocfentanil


Ortho-fluorofentanyl


Tetrahydrofuran-fentanyl



Wilde M, et al. (2019) Metabolic Pathways and Potencies of New Fentanyl Analogs. Front. Pharmacol. 10:238.doi: 10.3389/fphar.2019.00238

Opioid neuropharmacology

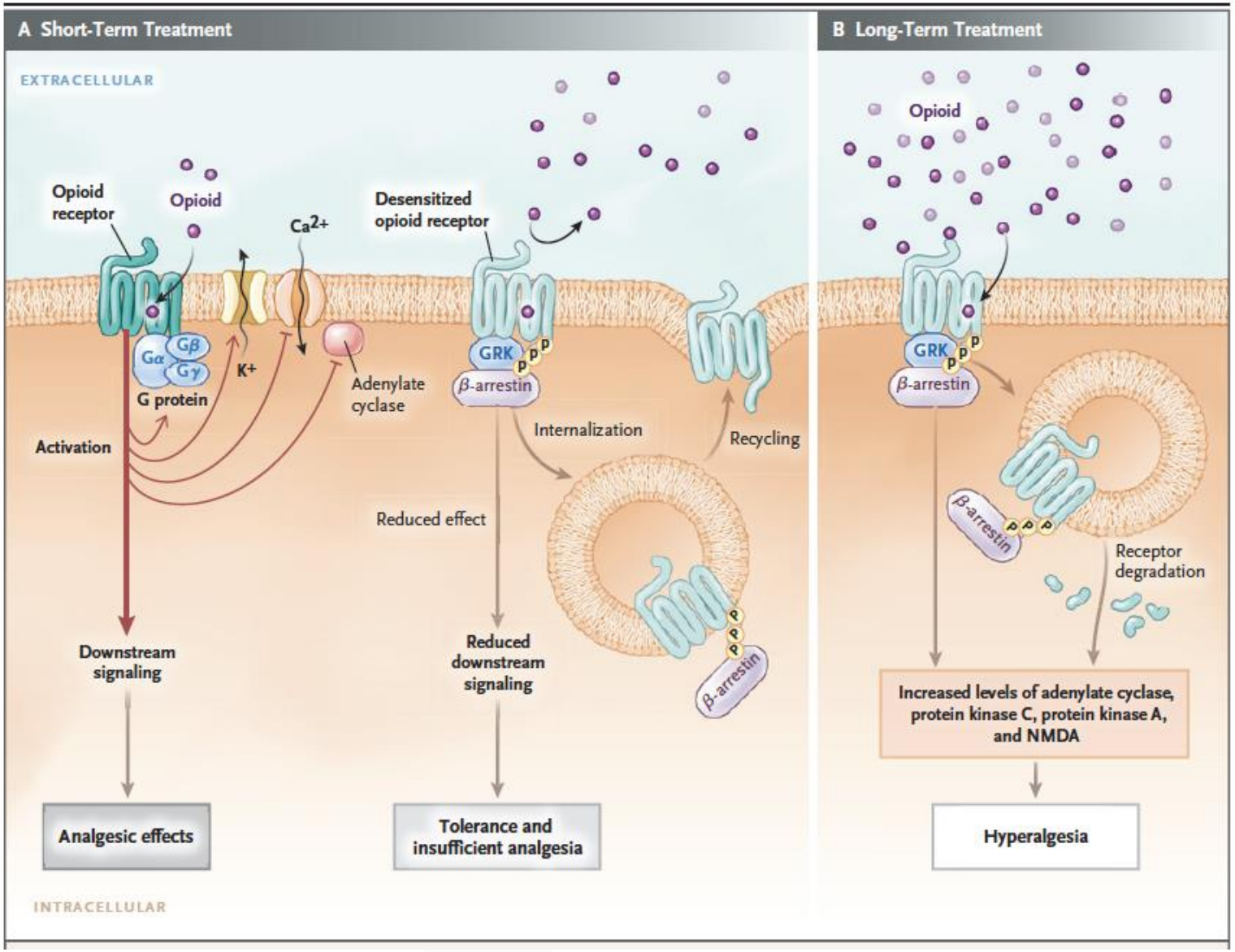
Opioid Agonists

OPIOID LIGANDS	RECEPTOR TYPES		
	μ	δ	κ
Etorphine	+++	+++	+++
Fentanyl	+++		
Hydromorphone	+++		+
Levorphanol	+++		
Methadone	+++		
Morphine[a]	+++		+
Sufentanil	+++	+	+
DAMGO[a] ([D-Ala^2,MePhe^4,Gly(ol)^5]enkephalin)	+++		
Bremazocine[c]	+	+	+++
Buprenorphine	P		– –
Butorphanol[c]	P		+++
Nalbuphine	– –		++
DPDPE[b] ([D-Pen2,5]-Enkephalin])	+++		
U50,488[c]		++	

+, agonist; −, antagonist; P, partial agonist. In potency: + < ++ < +++

Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13e > Opioids, Analgesia, and Pain Management

Neuropharmacology: opioid receptor signaling



Jeevendra Martyn et. al. (2019) Opioid Tolerance in Critical Illness
N Engl J Med 2019;380:365-78.DOI: 10.1056/NEJMra1800222

Fentanyl analogs – neuropharmacology

Fentanyl/ Fentanyl Analog	Binding Affinity to μ-Opioid Receptor (K_i)
Fentanyl	1.03 ± 0.15 nM
Carfentanil	0.024 ± 0.15 nM
Furanylfentanyl	0.028 ± 0.008 nM
Cyclopropylfentanyl	0.088 ± 0.027 nM
Tetrahyrofuranylfentanyl	0.95 ± 0.32nM
Butarylfentanyl	32 ± 4.1 nM

Wilde M, Pichini S, Pacifici R, Tagliabracci A, Busardò FP, Auwärter V and Solimini R (2019) Metabolic Pathways and Potencies of New Fentanyl Analogs. Front. Pharmacol. 10:238. doi: 10.3389/fphar.2019.00238

Fentanyl analogs – potencies & metabolites

Compounds	Detected metabolites (metabolic pathways)	Estimated relative potencies to fentanyl
Alfentanil	Noralfentanil (*N*-dealkylation)	Approximately 0.3
Sufentanil	Norsufentanil and *N*-phenylpropanamide (*N*-dealkylation), demethylsufentanil (*O*-demethylation), hydroxy metabolites	Approximately 10
Remifentanil	Remifentanil acid (ester hydrolysis)	Approximately 1
Acetylfentanyl	Acetyl norfentanyl (*N*-dealkylation), 4-ANPP (amide hydrolysis), β-hydroxyacetylfentanyl and further hydroxy metabolites, 4'-hydroxy-3'-methoxy-acetylfentanyl (dihydroxylation + methylation) and Phase II conjugates	0.3
Acryloylfentanyl	Acryloylnorfentanyl (*N*-dealkylation), 4-ANPP (amide hydrolysis), β-hydroxyacryloylfentanyl and further hydroxy metabolites, 4'-hydroxy-3'-methoxy-acryloylfentanyl (dihydroxylation + methylation) and phase II conjugates	Approximately 0.75
α-Methylfentanyl	Norfentanyl (*N*-dealkylation), Despropionyl-α-methylfentanyl (amide hydrolysis), Approximately 1 alkyl/aryl hydroxy metabolites	
Cis-3-methylfentanyl	Nor-3-methylfentanyl (*N*-dealkylation), alkyl/aryl hydroxy metabolites,	20 (+) isomer 0.2 (−) isomer
Trans-3-methylfentanyl	carboxypropionyl-3-methylfentanyl (hydroxylation + oxidations), 4^1-hydroxy-3^1-methoxy-3-methylfentanyl (dihydroxylation + methylation) and phase II conjugates	Approximately 1
Isofentanyl	Nor-3-methylfentanyl (*N*-dealkylation), alkyl/aryl hydroxy metabolites, carboxypropionyl-isofentanyl (hydroxylation + oxidations), 4^1-hydroxy-3^1-methoxy-isofentanyl (dihydroxylation + methylation), *N*-oxide formation and phase II conjugates	n.a.
Butyrfentanyl	Norbutyrfentanyl (*N*-dealkylation), carboxybutyrfentanyl (hydroxylation + oxidations), 4-ANPP (amide hydrolysis), alkyl/aryl hydroxy metabolites, 4^1-hydroxy-3^1-methoxy-butyrfentanyl (dihydroxylation + methylation), *N*-oxide formation and phase II conjugates	0.03–0.13
Isobutyrfentanyl	n.a.	0.13
Carfentanil	Norcarfentanil (*N*-dealkylation), alkyl/aryl hydroxy metabolites, carfentanil acid and phase-II conjugates	30–100

Wilde M, Pichini S, Pacifici R, Tagliabracci A, Busardò FP, Auwärter V and Solimini R (2019) Metabolic Pathways and Potencies of New Fentanyl Analogs. Front. Pharmacol. 10:238. doi: 10.3389/fphar.2019.00238

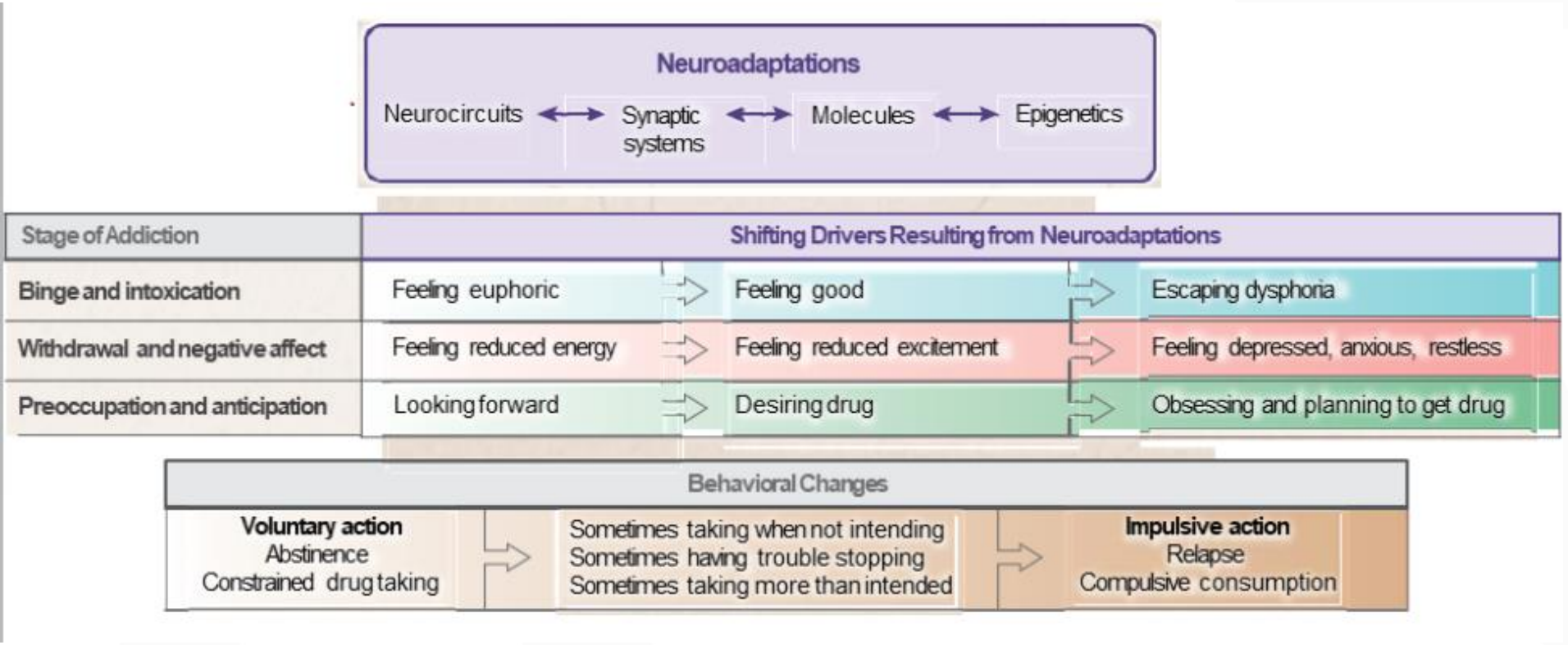
Fentanyl analogs – potencies & metabolites, cont.

Compounds	Detected metabolites (metabolic pathways)	Estimated relative potencies to fentanyl
Cyclopropylfentanyl	Norcyclopropylfentanyl (*N*-dealkylation), hydroxylations, dihydrodiol and *N*-oxide formation	3
Cyclobutylfentanyl	Norcyclobutylfentanyl (*N*-dealkylation), mainly alkyl hydroxy metabolites, 4-ANPP (amide hydrolysis), *N*-oxide and ketone formation	n.a.
Cyclopentylfentanyl	Norcyclopentylfentanyl (*N*-dealkylation), mainly alkyl hydroxy metabolites, 4-ANPP (amide hydrolysis), *N*-oxide and ketone formation	n.a.
Cyclohexylfentanyl	Norcyclohexylfentanyl (*N*-dealkylation), mainly alkyl hydroxy metabolites, 4-ANPP (amide hydrolysis), *N*-oxide and ketone formation	n.a.
2,2,3,3-Tetramethyl-cyclopropylfentanyl	Mainly alkyl hydroxy metabolites, Nor-2,2,3,3-tetramethylcyclopropylfentanyl (*N*-dealkylation), carboxy-2,2,3,3-tetramethylcyclopropylfentanyl (hydroxylation + oxidations)	n.a.
4-Fluoroisobutyrfentanyl	Nor-4-fluoroisobutyrfentanyl (*N*-dealkylation), alkyl/aryl hydroxy metabolites, 4-ANPP (amide hydrolysis), 4^1-hydroxy-3^1-methoxy-4-fluoroisobutyrfentanyl (dihydroxylation + methylation), dihydrodiol and ketone formation, carboxy-4-fluoroisobutyrfentanyl (hydroxylation + oxidations) and phase II conjugates	n.a.
Furanylfentanyl	Furano-dihydrodiol formation, 4-ANPP (amide hydrolysis), norfuranylfentanyl (*N*-dealkylation), alkyl/aryl hydroxy metabolites, ring opening of the furanyl ring and phase II conjugates	7
Methoxyacetylfentanyl	Demethylmethoxyacetylfentanyl (*O*-demethylation), 4-ANPP (amide hydrolysis), normethoxyacetylfentanyl (*N*-dealkylation), alkyl/aryl hydroxy metabolites and phase II conjugates	0.3
Ocfentanil	Demethylocfentanil (*O*-demethylation), alkyl/aryl hydroxy metabolites and phase II conjugates	2.5
Ortho-Fluorofentanyl	Nor-*ortho*-fluorofentanyl (*N*-dealkylation)	n.a.
Tetrahydrofuranylfentanyl	Nortetrahydrofuranylfentanyl (*N*-dealkylation), alkyl/aryl hydroxy metabolites, ring opening of the tetrahydrofuranyl ring and 4-ANPP (amide hydrolysis)	Approximately 0.2

Estimated relative potencies compared to fentanyl (set to 1) are also given (n.a., no data available).

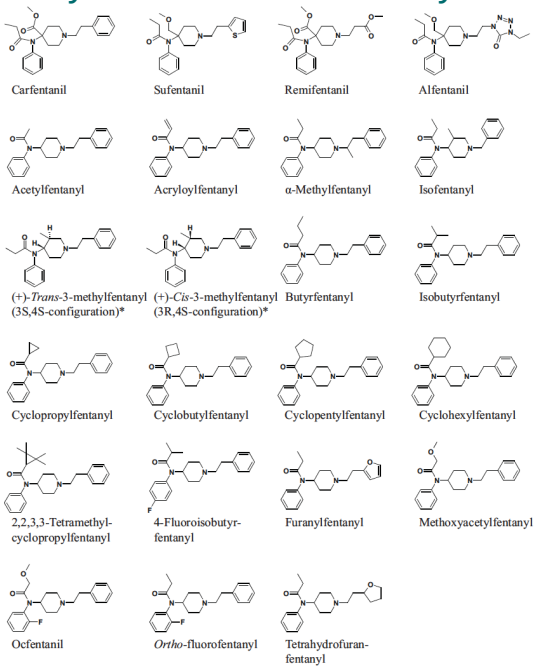
Wilde M, Pichini S, Pacifici R, Tagliabracci A, Busardò FP, Auwärter V and Solimini R (2019) Metabolic Pathways and Potencies of New Fentanyl Analogs. Front. Pharmacol. 10:238. doi: 10.3389/fphar.2019.00238

Brain Disease Model of Addiction

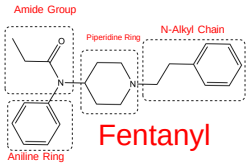


Volkow et. al. (2016) Neurological advances from the brain disease model of addiction.
N Engl J Med 2016;374:363-71. DOI: 10.1056/NEJMra1511480

Illicitly manufactured fentanyl and its analogs (IMFs)



The Problem



Source: US Drug Enforcement Agency (US DEA)
https://www.dea.gov/galleries/drug-images/fentanyl

Why?

- Avoid DEA controlled substance regulation
- Enhanced physiological/desired effects
  - Fentanyl 100x morphine
  - Carfentanil 10,000x morphine
- Avoid detection (Confirmation Assays)
- Synthesis is easy and does not require specialized technical knowledge
- Very, very lucrative!

Source: DEA

Source: Tennessee Bureau of Investigation

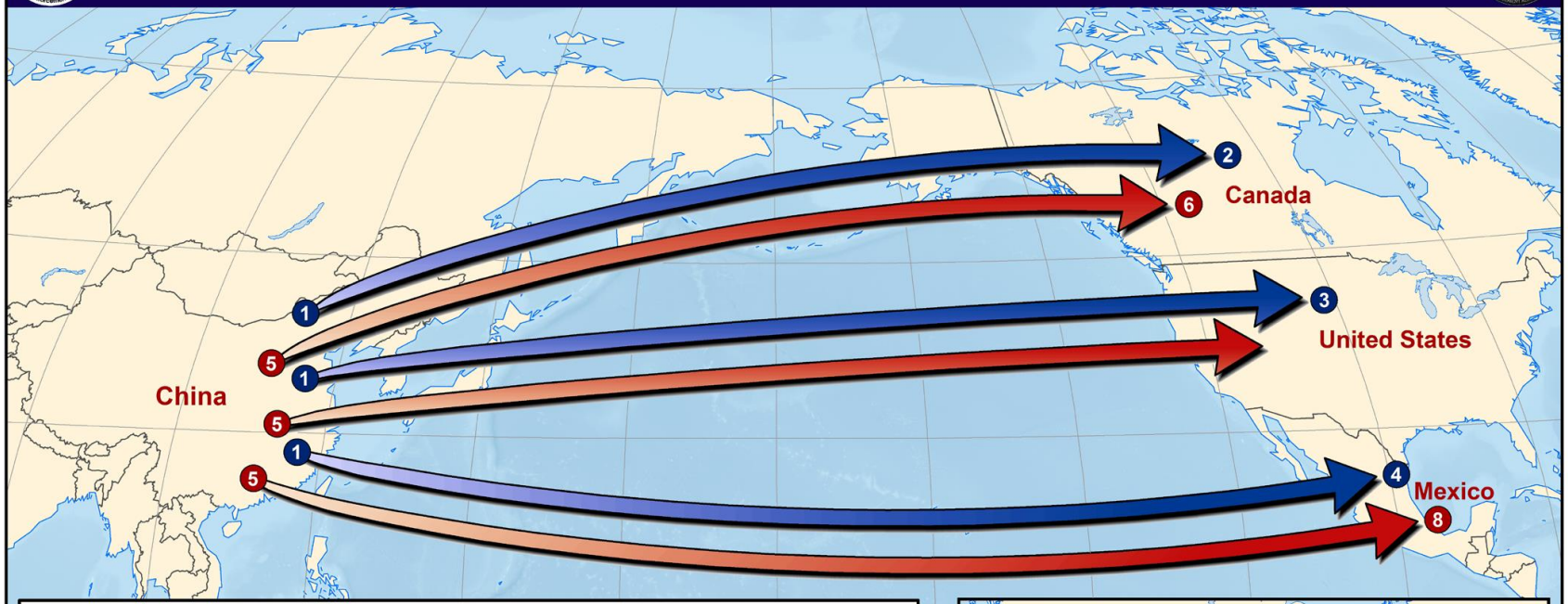
Potential Revenue Generated from Fentanyl Pill Sales Using 1 Kilogram of Fentanyl (in USC)

Amount of Fentanyl Per Pill	Price Per Pill	Price Per Pill	Price Per Pill
	$10	$15	$20
1.5 milligrams (666,666 pills)	$6.6 million	$9.9 million	$13.3 million
1 milligram (1 million pills)	$10 million	$15 million	$20 million

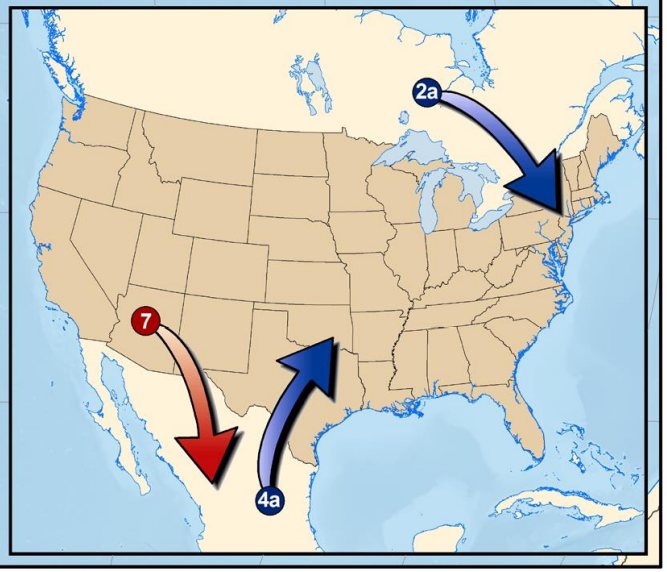
Source: DEA

Wilde M, et al. (2019) Metabolic Pathways and Potencies of New Fentanyl Analogs. Front. Pharmacol. 10:238.doi: 10.3389/fphar.2019.00238

(U) Illicit Fentanyl and Fentanyl Precursor Flow Originating in China



1. Fentanyls in powder form and pill presses are shipped via mail services.
2. The powder fentanyls are processed and mixed with heroin, or sold as heroin, or pressed into pills and sold in the Canadian drug market.
   - 2a. Some fentanyl products are smuggled from Canada into the United States for sale, on a smaller scale.
3. The powder fentanyls are processed and mixed with heroin, or sold as heroin, or pressed into pills and sold in the United States drug market.
4. The powder fentanyls are cut and diluted for further smuggling, or pressed into counterfeit prescription pills.
   - 4a. Diluted powder fentanyls and counterfeit prescription pills containing fentanyl are smuggled from Mexico into the United States.
5. Precursors for manufacturing fentanyls are shipped via mail services.
6. Precursors are used to manufacture fentanyls in clandestine laboratories.
7. Precursors are likely smuggled across the Southwest border into Mexico to manufacture fentanyls.
8. Precursors are likely used to manufacture fentanyls in clandestine laboratories.



List of fentanyl analogs[1]

No.	Compound Name
1	*para*-methoxy Butyryl fentanyl (hydrochloride)
2	Acetyl norfentanyl (hydrochloride)
3	α-methyl Acetyl fentanyl (hydrochloride)
4	Crotonyl fentanyl
5	Fentanyl
6	Acrylfentanyl (hydrochloride)
7	Cyclopropyl fentanyl (hydrochloride)
8	Isobutyryl fentanyl (hydrochloride)
9	Methoxyacetyl fentanyl (hydrochloride)
10	Valeryl fentanyl (hydrochloride)
11	(±)-*cis*-3-methyl Fentanyl (hydrochloride)
12	2'-fluoro *ortho*-Fluorofentanyl (hydrochloride)
13	*ortho*-Fluorobutyryl fentanyl (hydrochloride)
14	*ortho*-Fluorofentanyl (hydrochloride)
15	*ortho*-isopropyl Furanyl fentanyl
16	*ortho*-methyl Furanyl fentanyl (hydrochloride)
17	*ortho*-methyl Furanyl fentanyl
18	*meta*-Fluorobutyryl fentanyl (hydrochloride)
19	(±)-*cis*-3-methyl Butyryl fentanyl (hydrochloride)
20	4'-methyl Acetyl fentanyl (hydrochloride)
21	*para*-chloro Furanyl fentanyl
22	*para*-Methoxyfentanyl (hydrochloride)
23	*para*-methoxy Furanyl fentanyl (hydrochloride)
24	α-methyl Butyryl fentanyl (hydrochloride)
25	α-methyl Thiofentanyl (hydrochloride)
26	Benzodioxole fentanyl
27	Phenyl fentanyl (hydrochloride)
28	Benzyl fentanyl (hydrochloride)
29	N-benzyl Furanyl norfentanyl (hydrochloride)
30	Cyclohexyl fentanyl (hydrochloride)
31	Cyclopentyl fentanyl (hydrochloride)
32	*meta*-Methylfentanyl (hydrochloride)
33	N-methyl Norcarfentanil (hydrochloride)

No.	Compound Name
34	Norcarfentanil (hydrochloride)
35	*ortho*-methyl Acrylfentanyl (hydrochloride)
36	*ortho*-methyl Methoxyacetyl fentanyl (hydrochloride)
37	*para*-Chloroisobutyryl fentanyl (hydrochloride)
38	Tetrahydrofuran fentanyl (hydrochloride)
39	2,2,3,3-tetramethyl-Cyclopropyl f
40	Thienyl fentanyl (hydrochl
41	Thiophene fentan
42	Thiofentan
43	ortho
44	α'-n
45	α
46	
47	
48	
49	
5	
51	
53	
54	
55	
56	β
57	Et
58	Fent
59	Furany
60	Furanylethyl fe
61	Isovaleryl fentanyl (hy
62	*meta*-Fluoroisobutyryl fentan
63	*meta*-fluoro Methoxyacetyl fentanyl
64	*meta*-methyl Furanyl fentanyl (hydrochloride)
65	*meta*-methyl Methoxyacetyl fentanyl (hydrochloride)
66	Methacrylfentanyl

No.	Compound Name
67	*ortho*-fluoro Acrylfentanyl (hydrochloride)
68	*ortho*-fluoro Furanyl fentanyl (hydrochloride)
69	*ortho*-Fluoroisobutyryl fentanyl (hydrochloride)
70	*ortho*-methoxy Butyryl fentanyl (hydrochloride)
71	*ortho*-methyl Cyclopropyl fentanyl (hydrochloride)
	ethylfentanyl (hydrochloride)
	henyl fentanyl (hydrochloride)
	drochloride)
	drochloride)
	loride)
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	hloride)
	loride)
	drochloride)
	pyl fentanyl (hydrochloride)
	ranyl fentanyl (hydrochloride)
	ethyl Isobutyryl fentanyl (hydrochloride)
101	*para*-methyl Methoxyacetyl fentanyl (hydrochloride)
102	*para*-methyl Tetrahydrofuran fentanyl (hydrochloride)
103	Phenylacetyl fentanyl (hydrochloride)

No.	Compound Name
104	Pivaloyl fentanyl (hydrochloride)
105	Remifentanil (hydrochloride)
106	Sufentanil
107	Tetrahydrofuran fentanyl 3-tetrahydrofurancarboxamide (hydrochloride)
108	(±)-*cis*-3-methyl Thiofentanyl (hydrochloride)
109	β-Hydroxythiofentanyl (hydrochloride)
110	Norfentanyl
111	4-ANPP
112	β-methyl Fentanyl (hydrochloride)
113	(±)-*trans*-3-methyl Fentanyl (hydrochloride)
114	*para*-Fluorobutyryl fentanyl (hydrochloride)
115	FIBF (hydrochloride)
116	α-methyl Fentanyl (hydrochloride)
117	Ocfentanil (hydrochloride)
118	*para*-Fluorofentanyl (hydrochloride)
119	Butyryl norfentanyl (hydrochloride)
120	Butyryl fentanyl (hydrochloride)
121	Furanyl fentanyl (hydrochloride)
122	Acetyl fentanyl (hydrochloride)
123	4'-Fluorofentanyl (hydrochloride)
124	4-Phenyl fentanyl (hydrochloride)
125	Cyclopentenyl fentanyl (hydrochloride)
126	*para*-methyl Cyclopentyl fentanyl (hydrochloride)
127	*meta*-methyl Cyclopropyl fentanyl (hydrochloride)
128	*para*-methyl Butyryl fentanyl (hydrochloride)
129	*para*-methoxy Acetyl fentanyl (hydrochloride)
130	*para*-methoxy Methoxyacetyl fentanyl (hydrochloride)
131	Tetrahydrothiophene fentanyl
132	N,N-Dimethylamido-despropionyl fentanyl
133	Hexanoyl fentanyl (hydrochloride)
134	Heptanoyl fentanyl (hydrochloride)
135	β-Hydroxythioacetylfentanyl
136	2,3-seco-Fentanyl (hydrochloride)
137	Senecioylfentanyl
138	Phenoxyacetyl fentanyl (hydrochloride)
139	Fentanyl Methyl Carbamate
140	β-hydroxy Fentanyl (hydrochloride)

US DEA

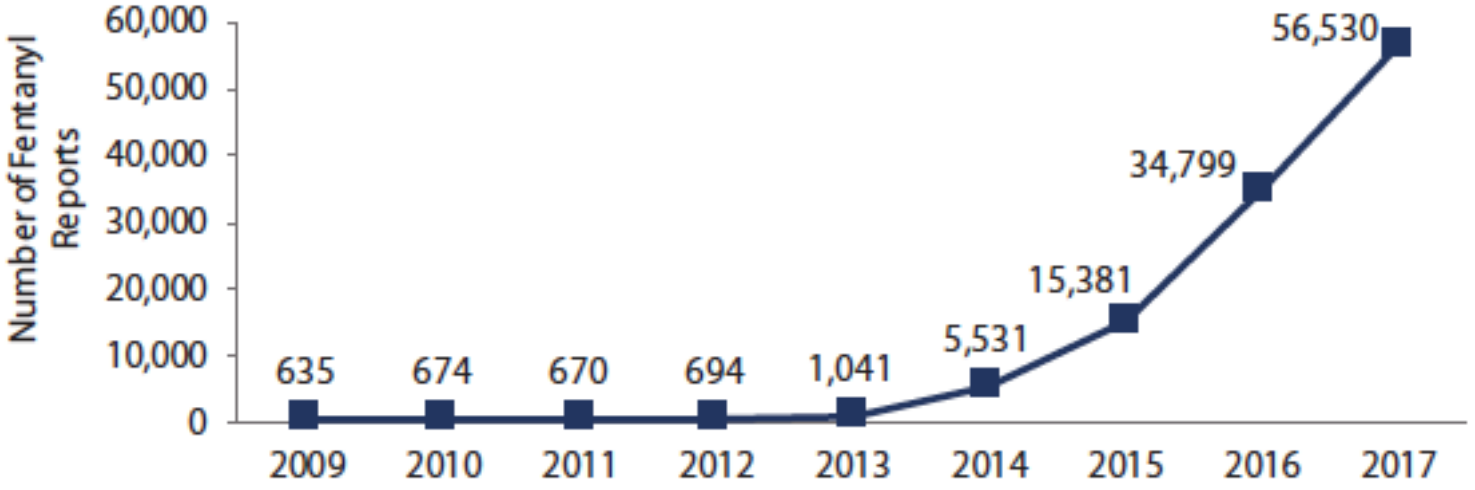
All fentanyl-related substances "temporarily" placed on Schedule I list[2] until Feb 6, 2020.

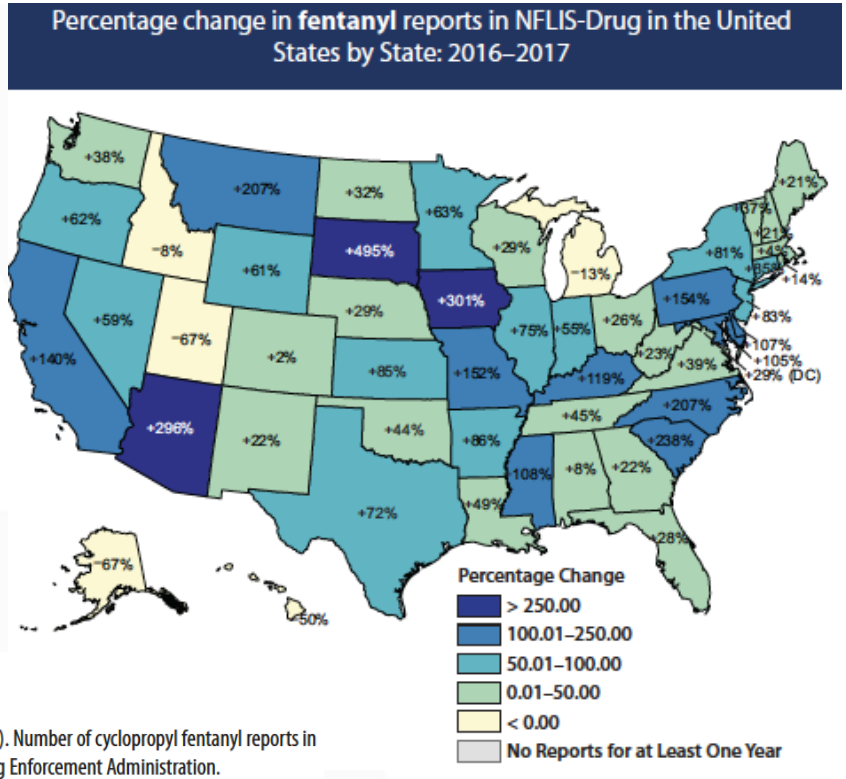
SOFA Act

1: Cayman Chemical

2: Schedules of Controlled Substances: Temporary Placement of Fentanyl Related Substances in Schedule I.
Federal Register / Vol. 83, No. 25 / Tuesday, February 6, 2018 / Rules and Regulations

NFLIS: Tracking Fentanyl Analogs

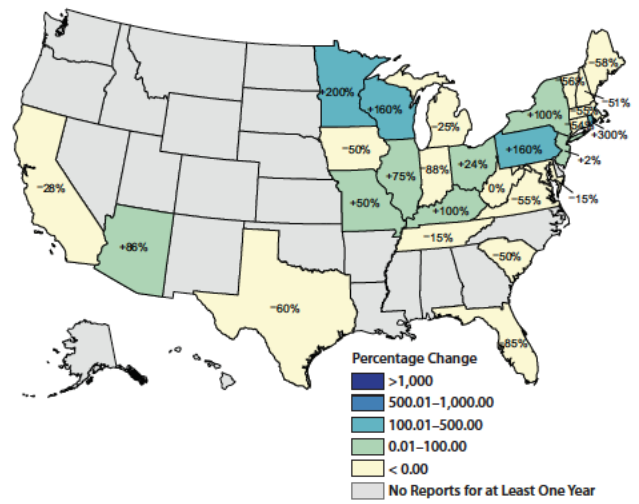




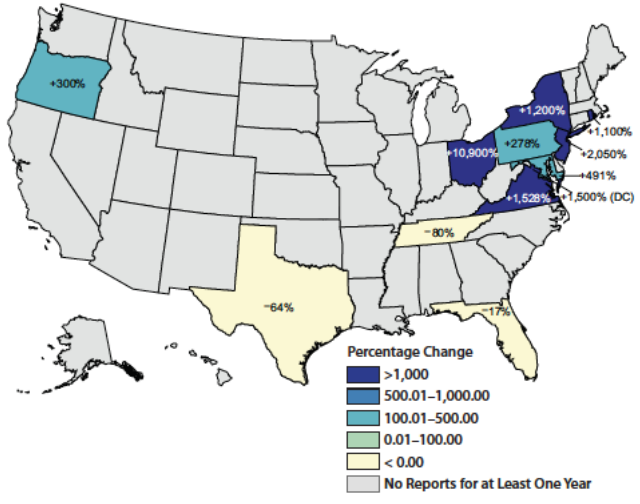
U.S. Drug Enforcement Administration, Diversion Control Division. (2018). Number of cyclopropyl fentanyl reports in NFLIS-Drug in the United States by State: 2017. Springfield, VA: U.S. Drug Enforcement Administration.

NFLIS: Tracking Fentanyl Analogs

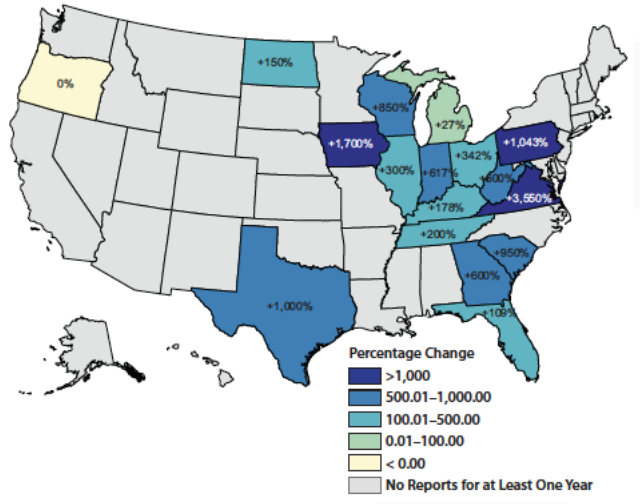
Percentage change in **acetyl fentanyl** reports in NFLIS-Drug in the United States by State: 2016–2017



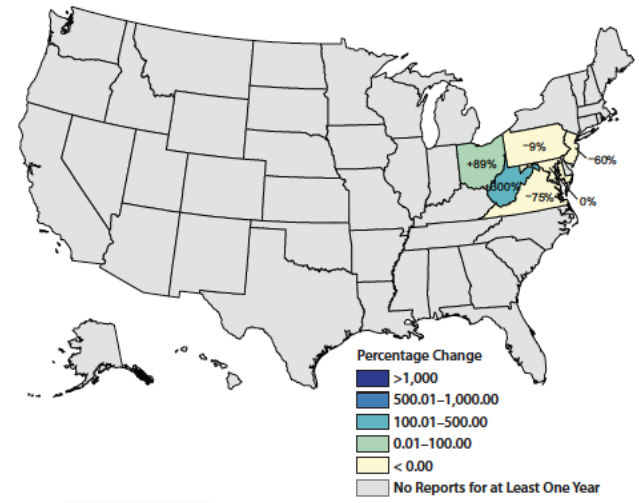
Percentage change in **4-fluoroisobutyryl fentanyl** reports in NFLIS-Drug in the United States by State: 2016–2017



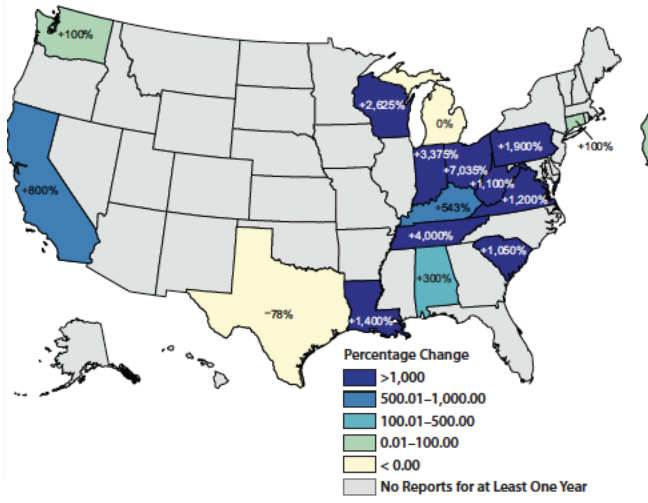
Percentage change in **carfentanil** reports in NFLIS-Drug in the United States by State: 2016–2017



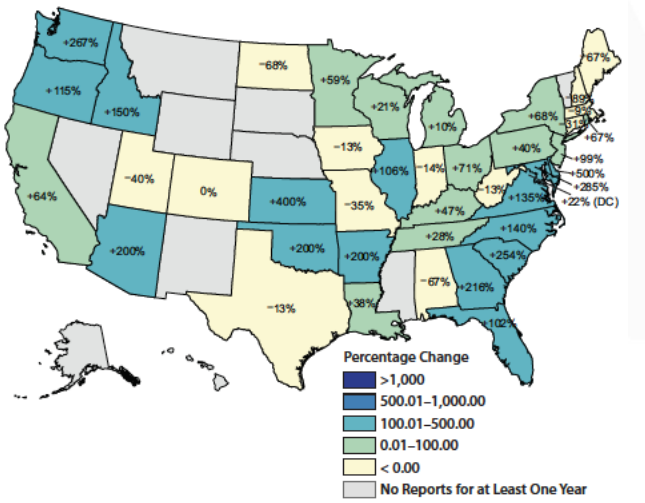
Percentage change in **3-methylfentanyl** reports in NFLIS-Drug in the United States by State: 2016–2017



Percentage change in **acryl fentanyl** reports in NFLIS-Drug in the United States by State: 2016–2017

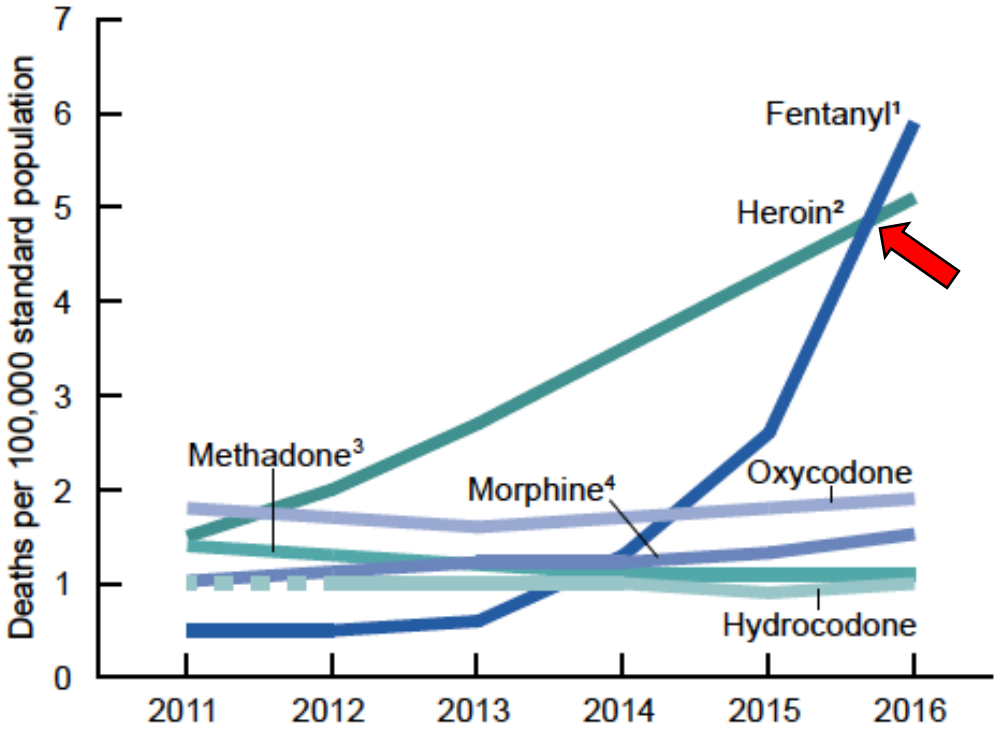


Percentage change in **furanyl fentanyl** reports in NFLIS-Drug in the United States by State: 2016–2017



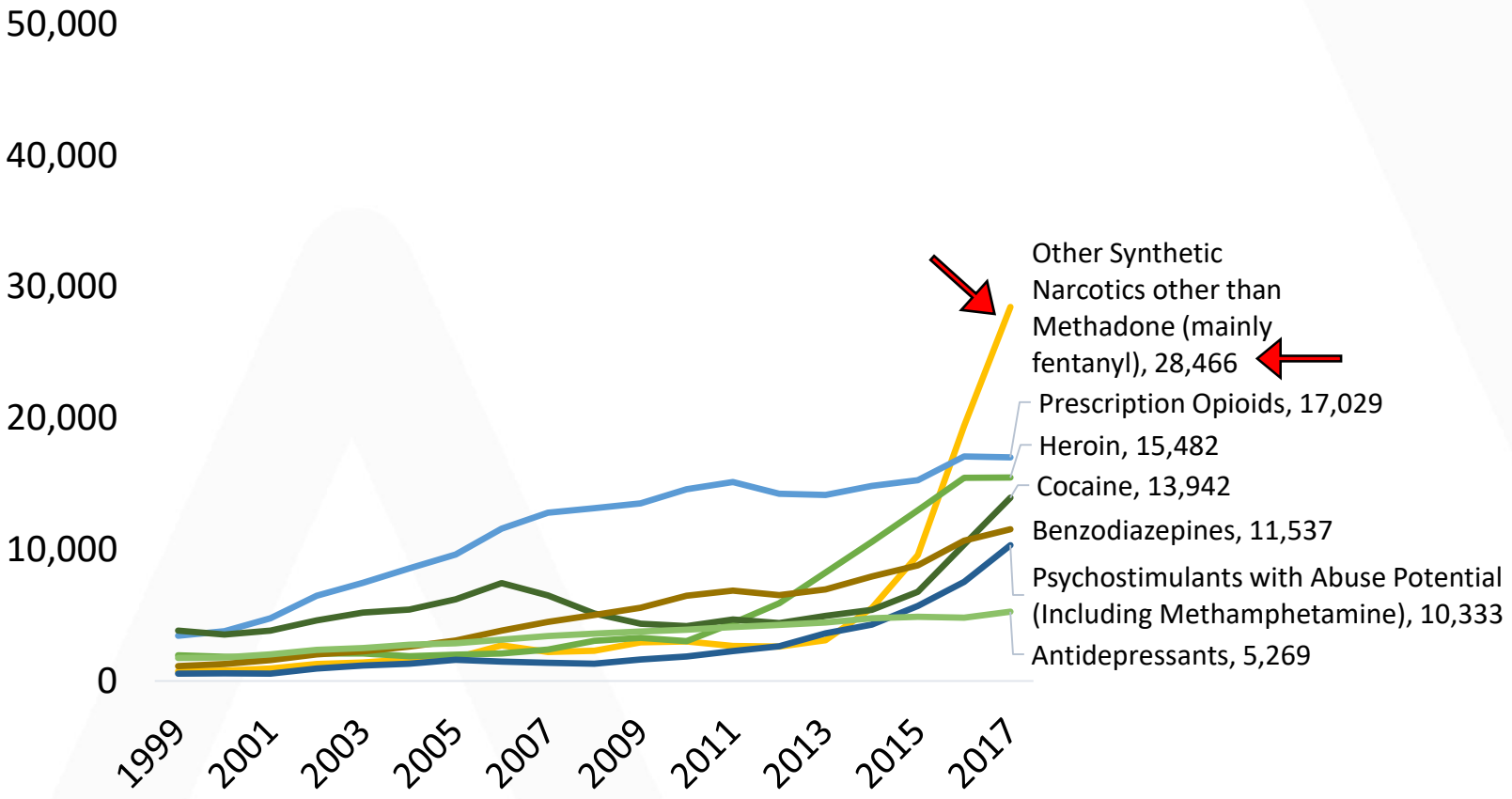
U.S. Drug Enforcement Administration, Diversion Control Division. (2018). Number of cyclopropyl fentanyl reports in NFLIS-Drug in the United States by State: 2017. Springfield, VA: U.S. Drug Enforcement Administration.

Statistics: National Overdose Deaths



National Vital Statistics Reports, Vol. 67, No. 9, December 12, 2018

Statistics: **National Drug Overdose Deaths** Number Among All Ages, 1999-2017



Source: : Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2017 on CDC WONDER Online Database, released December, 2018

Fentanyl analogs: common characteristics, street names, means of use, and intentional use

Typology	Most Famous Brand Names	Forms in Which Found on the Market
Novel Fentanyl derivatives	Usually added to or substituted for heroin, often without the user's knowledge; e.g., acetylfentanyl, butyrylfentanyl, furanyl fentanyl, 4methyl fentanyl and other forms; usually not approved for medical use	Powders (usually mixed with heroin or other illicit drugs), tablets (counterfeit prescriptions pills), nasal sprays, liquids.
Non-medical fentanyl, illicitly manufactured fentanyl	"China White", "Synthetic Heroin", "China Girl", "Chinatown", "Tango & Cash", "TNT", "Drop Dead", "Flatline", "Lethal Injection", "Poison", "Apache", "Dance Fever", "Great Bear", "Perc-o-Pops", "Lollipops".	Tablets: buccal (Fentora™) and sublingual (Abstral®); oral transmucosal lozenges (Actiq®), film Onsolis®, spray: sublingual (Subsys™) and nasal (Lazanda®); transdermal patches (Ionsys®, (Duragesic® and generics; brand names: Duragesic, Duragesic Mat, Ionsys, Fentanyl Transdermal System Novaplus), injectable formulations (Sublimaze®).

Typology	Means of Use	Neurobiology
Non-medical fentanyl, illicitly manufactured fentanyl	Transdermal fentanyl patches: smoked (placed in glass containers and heated or fentanyl scratched) or taken intranasally (fentanyl powder snorted); parenterally or orally (gel contents removed from the patches, oral ingestion of lozenges); parenteral (patches simmered in a water and injected intravenously, intramuscularly); frozen patches cut into pieces and then chewed, placed under the tongue, or in the cheek cavity for drug absorption through the oral mucosa or inserted into the rectum.	Binds to mu-receptor but also to kappa and delta-type opioid receptors.
Novel Fentanyl derivatives	Orally, sublingual application, nasally—by smoking or by nasal insufflation, intrarectally, intravenous , intramuscular injection or by combinations of these routes.	Acts primarily on the mu (plus some kappa and some delta) opioid receptors.

Typology	Intentionality of Use
Non-medical fentanyl, illicitly manufactured fentanyl	Yes
Novel Fentanyl derivative	Not for fentanyl analogues—usually added to heroin or other illicit drugs, often without the user's knowledge.

Lovrecic et. al. (2019) Non-Medical Use of Novel Synthetic Opioids: A New Challenge to Public Health
Int. J. Environ. Res. Public Health.16, 177; doi:10.3390/ijerph16020177

Current state of fentanyl/analogs detection methodologies

Screening (Immunalysis)

- Immunoassay: Fentanyl
- Cross-reactivity: Significant cross-reactivity with acrylfentanyl, cyclopropylfentanyl, tetrahydrofuranylfentanyl and 4-fluroisobutarylfentanyl
- No cross-reactivity with carfentanil

Confirmation (LC-MS/MS)

- Traditional routine confirmation assays test for Fentanyl/Norfentanyl
- Some lab may offer acetylfentanyl/Noracetylfentanyl as part of routine confirmation test
- Very few laboratories offer specialty fentanyl analogs confirmation assay
- Matrix: Mostly blood and urine
- Forensic analysis usually have the most comprehensive testing and identification of fentanyl analogs
- Clinical urine samples routine testing of fentanyl analogs ?

Guerrieri et. al. (2018) Validation and Cross-Reactivity Data for Fentanyl Analogs With the Immunalysis Fentanyl ELISA
Journal of Analytical Toxicology, 2018;1–7. doi: 10.1093/jat/bky060

Clinical Case Study

Opioid Dependence

- 40-year-old male diagnosed with opioid dependence
- Enrolled in a suboxone treatment plan
- Urine sample drug screening (Immunoassays)
  - Positive for 6-acetylmorphine, benzodiazepines, cocaine, fentanyl and opiates
- Confirmation Test (LC-MS/MS)
  - Traditional confirmation assay will test for fentanyl/norfentanyl

Clinical Case Study, cont.

Patient		Matrix - Urine		Provider	
Name	Urgent, Help	Accession #	1112-1	Doctor	Test
ID	444-4	Collection Date	5/13/2019 6:20 AM	Organization	AcutisDiagnostics
Gender	Male	Received Date	5/17/2019		
Birth	10/19/1978	Reported Date	5/20/2019		

Summary

Prescribed drug found (CONSISTENT) - Parent drug or metabolite was detected

Reported Prescription	Anticipated Positives(s)	Test Outcome	Detection Window
N/A	N/A	N/A	N/A

Prescribed drug not found (INCONSISTENT) - Parent drug or metabolite was not detected

Reported Prescription	Anticipated Positive(s)	Test Outcome	Detection Window
Suboxone	Buprenorphine	NEGATIVE	2 - 24 hours
	↳ Norbuprenorphine	NEGATIVE	2 - 48 hours
	↳ Naloxone	NEGATIVE	1 - 3 days

Non-prescribed drug found (INCONSISTENT) - Suggests illicit or non-prescribed drug taken

Detected Analyte	Illicit	Result	Cutoff	Test Outcome	Detection Window
Morphine	No	1131	50	POSITIVE	1 - 3 days
Fentanyl	No	741	5	POSITIVE	1 - 3 days
Norfentanyl	No	>1000	5	POSITIVE	1 - 3 days
Lorazepam	No	>500	50	POSITIVE	1 - 5 days
Heroin Metabolite - 6-AM	Yes	21	10	POSITIVE	1 - 2 days
Cocaine Metabolite - BE	Yes	>1000	50	POSITIVE	1 - 5 days

Specimen validity testing

Test	Test Outcome	Result	Reference Range

Medication Prescribed but not tested

None

Historical results	5/13/2019	4/9/2019			
Prescribed drug found					
Prescribed drug not found	Suboxone				
Non-prescribed or illicit drug found	Heroin Metabolite - 6-AM, Cocaine Metabolite - BE, Fentanyl, Lorazepam, Morphine, Norfentanyl	Cocaine Metabolite - BE, Fentanyl, Hydromorphone, Lorazepam, Norfentanyl, Pregabalin			

↳ Indicates drug metabolite or additional drug component. Relationship is not shown for any non-prescribed drugs found.

Clinical Case Study, cont.

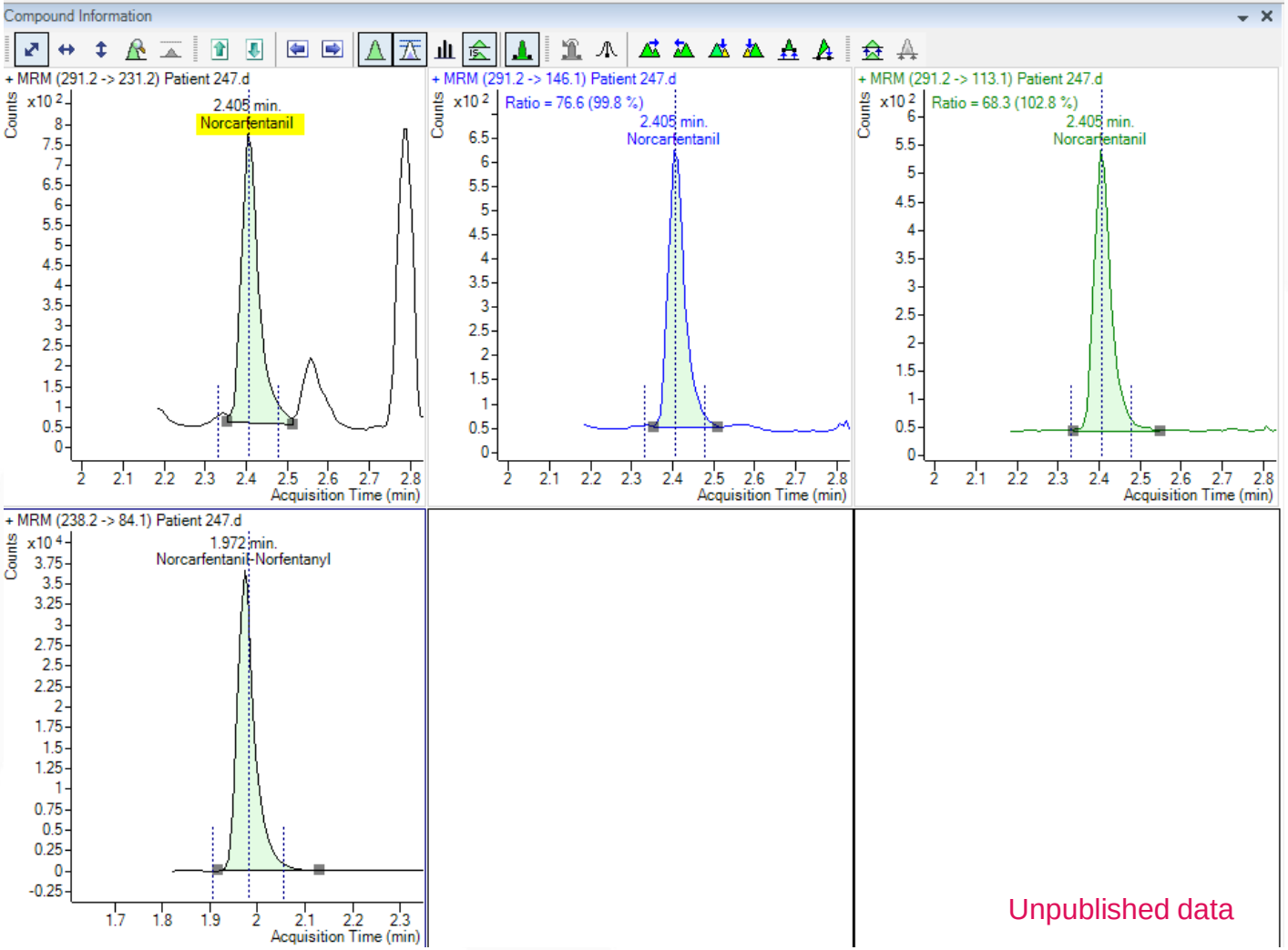
Patient		Matrix - Urine		Provider	
Name	Urgent, Help	Accession #	1112-1	Doctor	Test
ID	444-4	Collection Date	5/13/2019 6:20 AM	Organization	AcutisDiagnostics
Gender	Male	Received Date	5/17/2019		
Birth	10/19/1978	Reported Date	5/20/2019		

Detailed

Test Name	Outcome	Result [ng/mL]	Cutoff	Detection Window	Status
Natural & Semi-Synthetic Opiates					
Codeine	Negative	-	50	1 - 3 days	Consistent result
Morphine	**Positive**	**1131**	**50**	**1 - 3 days**	**Inconsistent result**
Hydrocodone	Negative	-	50	1 - 3 days	Consistent result
Hydromorphone	Negative	-	50	1 - 3 days	Consistent result
Norhydrocodone	Negative	-	50	1 - 3 days	Consistent result
Dihydrocodeine	Negative	-	50	1 - 3 days	Consistent result
Oxycodone	Negative	-	50	1 - 3 days	Consistent result
Noroxycodone	Negative	-	50	1 - 3 days	Consistent result
Oxymorphone	Negative	-	50	1 - 3 days	Consistent result
Buprenorphine	**Negative**	**-**	**10**	**2 - 24 hours**	**Inconsistent result**
Norbuprenorphine	**Negative**	**-**	**10**	**2 - 48 hours**	**Inconsistent result**
Naloxone	**Negative**	**-**	**10**	**1 - 3 days**	**Inconsistent result**
The poppy plant produces morphine and codeine. Ingestion of bakery products containing poppy seeds can cause morphine, and to a lesser extent codeine, to be excreted in urine. If excessively large amounts are consumed, this can result in urine morphine concentrations up to 2000 ng/mL for a period of 6 to 12 hours following ingestion.					
Synthetic Opioids					
Fentanyl	**Positive**	**741**	**5**	**1 - 3 days**	**Inconsistent result**
Norfentanyl	**Positive**	**>1000**	**5**	**1 - 3 days**	**Inconsistent result**
Benzodiazepines					
Alprazolam	Negative	-	25	1 - 3 days	Consistent result
Alpha-Hydroxyalprazolam	Negative	-	25	1 - 3 days	Consistent result
Clonazepam	Negative	-	25	<1 day	Consistent result
7-Aminoclonazepam	Negative	-	25	1 - 5 days	Consistent result
Diazepam	Negative	-	25	1 - 10 days	Consistent result
Nordiazepam	Negative	-	25	1 - 10 days	Consistent result
Temazepam	Negative	-	25	1 - 5 days	Consistent result
Oxazepam	Negative	-	50	1 - 5 days	Consistent result
2-Hydroxyethylflurazepam	Negative	-	50	1 - 2 days	Consistent result
Lorazepam	**Positive**	**>500**	**50**	**1 - 5 days**	**Inconsistent result**
Alpha-Hydroxymidazolam	Negative	-	50	1 - 3 days	Consistent result
Anti-Epileptics					
Gabapentin	Negative	-	1000	1 - 7 days	Consistent result
Pregabalin	Negative	-	1000	1 - 7 days	Consistent result
Illicit Drugs					
Heroin Metabolite - 6-AM	**Positive**	**21**	**10**	**1 - 2 days**	**Inconsistent result**
Cocaine Metabolite - BE	**Positive**	**>1000**	**50**	**1 - 5 days**	**Inconsistent result**
PCP	Negative	-	25	1 - 8 days	Consistent result
MDMA	Negative	-	50	2 - 72 hours	Consistent result

Clinical Case Study: Fentanyl Analogs LC-MS/MS

Name	Transition	User Defined 4	RT	Resp.	MI	Calc. Conc.	Final Conc.	Accuracy	Transition	Ratio	MI	Transition	R
Norfent	233.2 -> 84.1		2.007	9702015		277.4576	277.4576		233.2 -> 55.1	27.7		233.2 -> 150.1	
Fent	337.2 -> 188.1		3.423	16812723		220.1403	220.1403		337.2 -> 105.1	89.7			
Acetyl norfentanyl	219.1 -> 84.1		1.070	2035367		38.9550	38.9550		219.1 -> 55.1	29.0		219.1 -> 94.1	
Acetyl fentanyl	323.2 -> 105.1		2.825	1181733		17.5563	17.5563		323.2 -> 188.1	101.3			
4-ANPP	281.2 -> 188.1		2.995	611296		4.4318	4.4318		281.2 -> 105.0	89.1		281.2 -> 77.1	
Norcarfentanil	291.2 -> 231.2		2.405	2123		0.2333	0.2333		291.2 -> 146.1	76.6		291.2 -> 113.1	
Acryl fentanyl	335.2 -> 188.1		3.279	23063		0.1619	0.1619		335.2 -> 105.1	101.5			
Carfentanil	395.2 -> 335.2		3.696	3806		0.0210	0.0210		395.2 -> 113.0	34.2			



Unpublished data

Harm reduction technologies

Overdose Education and Naloxone Distribution (OEND) Programs

- Naloxone can effectively reverse respiratory depression caused by overdose of many opioids. It is a pure antagonist at μ-opioid receptor.

- Overdose victims cannot administer naloxone to themselves; therefore, bystander naloxone administration (BNAL) is predicated on the assumption that a willing layperson witnesses or discovers an overdose victim, has access to a take-home naloxone (THN) kit, and the knowledge to use it.

- Since 1996, OEND programs have provided persons who use opioids and laypersons (e.g. family members and peers) with training to recognize the signs and symptoms of opioid overdose and to administer THN.

- Studies have shown that with training, they can recognize the signs of opioid overdose and administer naloxone successfully.

- THN Kits
  - Evzio intramuscular (IM) auto-injector device ($ 4000 contains two IM kits) 2mg/0.4mL; 98.3% bioavailability
  - Narcan® intranasal kit ($ 130 contains two kits) 4mg/0.1mL; 46.2% bioavailability
  - 48 states allow purchase of naloxone without a prescription through a standing order for naloxone

- Limitations:
  - Social stigma and misconceptions
  - Cost of naloxone kits/ out-of-pocket
  - Laypersons' access to THN kits remains limited

Hong K. Kim, Nicholas J. Connors & MaryAnn E. Mazer-Amirshahi (2019): The role of take-home naloxone in the epidemic of opioid overdose involving illicitly manufactured fentanyl and its analogs, Expert Opinion on Drug Safety, DOI: 10.1080/14740338.2019.1613372

Harm reduction technologies, cont.

Use of rapid fentanyl test strips

- Willingness to use rapid test strips regardless of having ever overdosed, suggesting that rapid fentanyl testing is an acceptable harm reduction intervention among young people

Krieger et al. Harm Reduction Journal (2018) 15:7 https://doi.org/10.1186/s12954-018-0213-2

Users' perception of fentanyl adulterated and substituted heroin

- Determining fentanyl's presence, followed by taste, solution appearance and powder color.
- A new 'heroin' typology based on users' reports
- If validated, this typology would be a valuable harm reduction tool

Ciccarone et al. Heroin uncertainties: exploring users' perceptions of fentanyl-adulterated and -substituted 'heroin'. Int J Drug Policy. 2017 August ; 46: 146–155. doi:10.1016/j.drugpo.2017.06.004.

Non-prescription over-the-counter (OTC) Naloxone availability (in the works)

- To address public health crisis, the FDA is facilitating the development of labeling for the OTC version of naloxone

FDA. Comprehension for OTC Naloxone (CONFER) Pivotal Label Comprehension Study – Task 3 Study Report

Fentanyl/fentanyl analogs overdose treatment

- Fentanyl and its analogs are highly lipophilic, allowing them to achieve rapid steady-state equilibrium between plasma and cerebrospinal fluid
- Rapid onset of life-threatening respiratory depression (2 minutes for fentanyl)
- Fentanyl analogs with lower potency/lipophilicity have increased risk of overdose death prior to THN administration by a bystander
- There is limited documented experience in the reversal of fentanyl analogs' overdose
- Single dose of naloxone may not reverse opioid toxicity in all suspected overdose victims, especially when the specific agent and its dose are unknown
- Unpredictable drug kinetic could result in recurrence of ventilatory depression
- A longer observation period may be required
- Between 2015 and 2017, higher doses of PNK were administered to reverse opioid toxicity, while the reversal rate declined. This suggests that higher doses of naloxone might be required to reverse opioid toxicity in people in whom overdose with synthetic opioids/fentanyl is suspected.

Hong K. Kim, Nicholas J. Connors & MaryAnn E. Mazer-Amirshahi (2019): The role of take-home naloxone in the epidemic of opioid overdose involving illicitly manufactured fentanyl and its analogs, Expert Opinion on Drug Safety, DOI: 10.1080/14740338.2019.1613372

Sarah G. Mahonski, James B. Leonard, J. David Gatz, Hyunuk Seung, Erin E. Haas & Hong K. Kim (2019): Prepacked naloxone administration for suspected opioid overdose in the era of illicitly manufactured fentanyl: a retrospective study of regional poison center data, Clinical Toxicology, DOI:10.1080/15563650.2019.1615622

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Conclusion and take-home points

- Neuropharmacology and pharmacokinetics of synthetic cannabinoids and fentanyl analogs' addictive potential
- Differences between various synthetic cannabinoids and fentanyl analog products
- Review the statistics and prevalence of synthetic cannabinoids and fentanyl analogs amongst commonly abused substances
- Review the current state of detection methodologies to detect synthetic cannabinoids and fentanyl analogs
- Review the harm reduction technologies and overdose treatments

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Next steps

- To ask follow-up questions:

  karnold@acutis.com