Not Your Father's Heroin:
Forensic Toxicology in the Age of Fentanyl and Fentanyl Analogs

Presented by:
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Opioids were involved in 33,091 deaths in 2015

Overdoses involving opioids have quadrupled since 1999

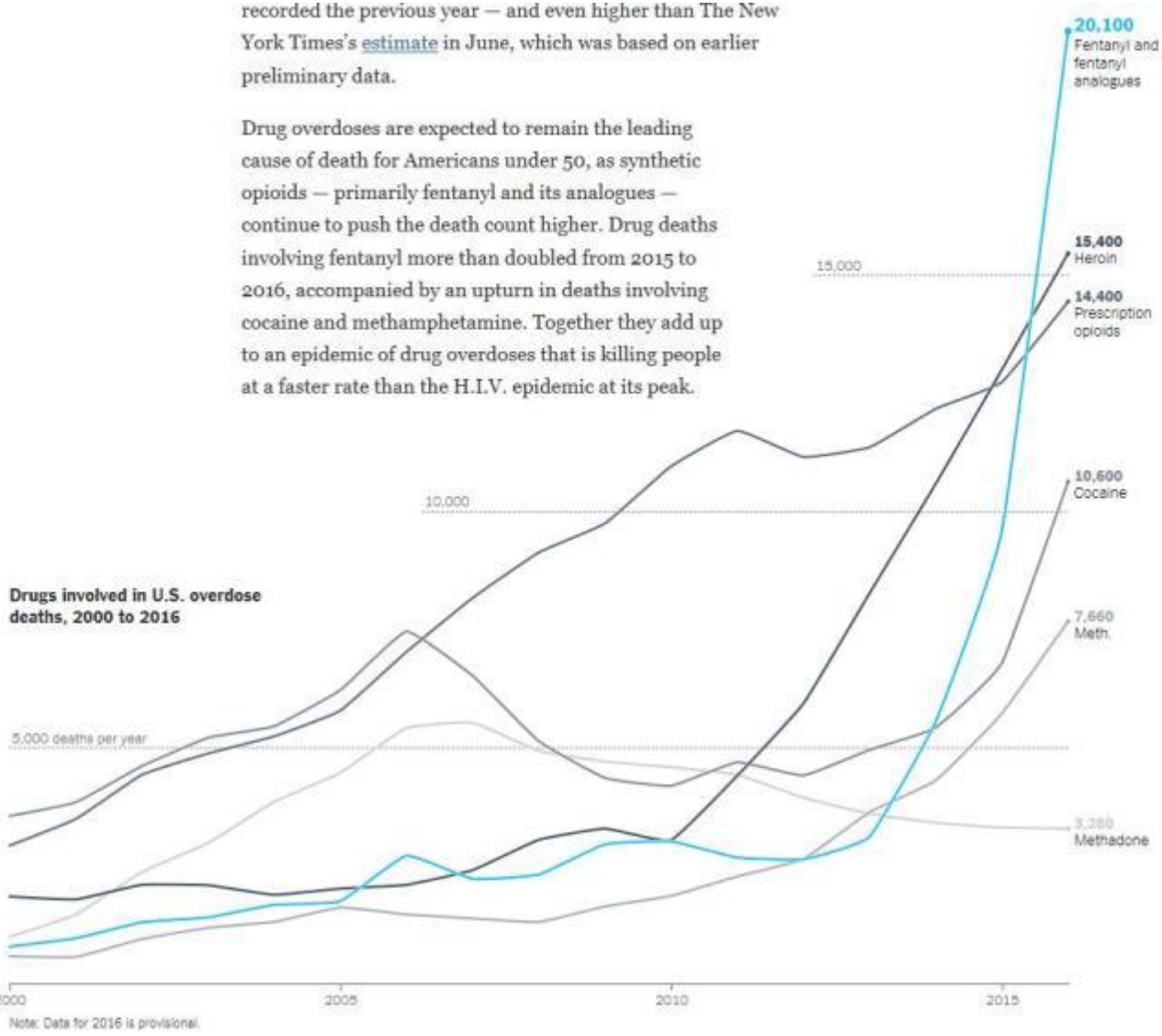
Highest rates of death due to drug OD:

West Virginia (41.5/100,000)
New Hampshire (34.3/100,000)
Kentucky (29.9/100,000)
Ohio (29.9/100,000)
Rhode Island (28.2/100,000)

19 states saw statistically significant increases in death rates from 2014 to 2015

recorded the previous year — and even higher than The New York Times's estimate in June, which was based on earlier preliminary data.

Drug overdoses are expected to remain the leading cause of death for Americans under 50, as synthetic opioids — primarily fentanyl and its analogues — continue to push the death count higher. Drug deaths involving fentanyl more than doubled from 2015 to 2016, accompanied by an upturn in deaths involving cocaine and methamphetamine. Together they add up to an epidemic of drug overdoses that is killing people at a faster rate than the H.I.V. epidemic at its peak.

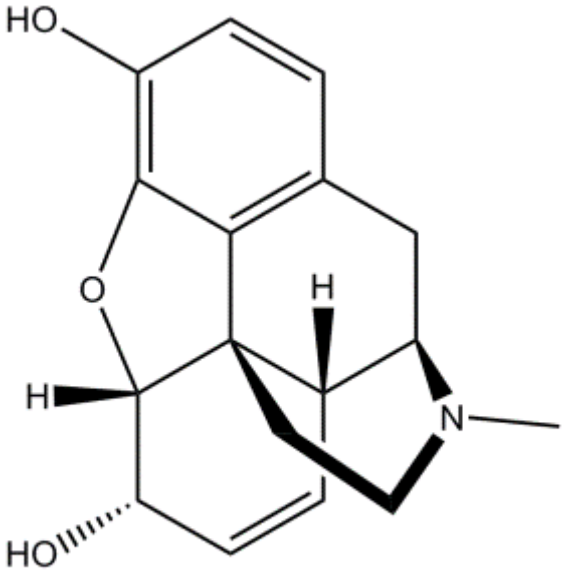


New York Times, 9/2/2017

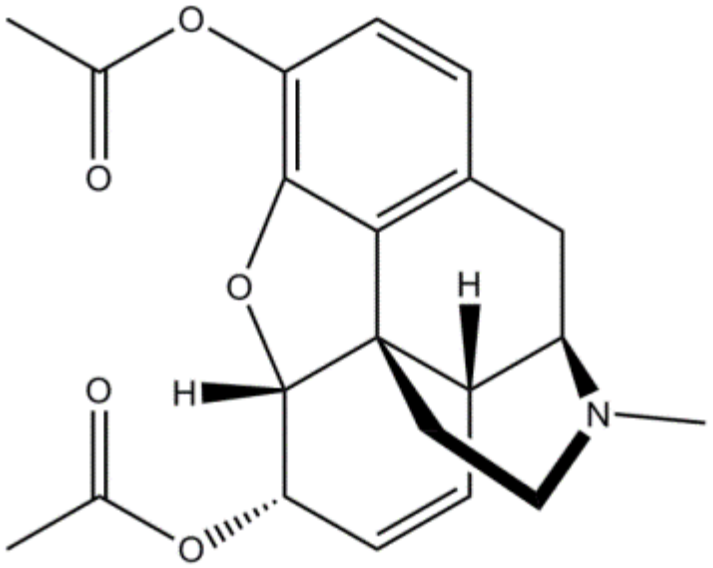
Heroin

Originally synthesized in the 1870s in London, England

Non-addictive form of morphine - Diacetylmorphine



Morphine

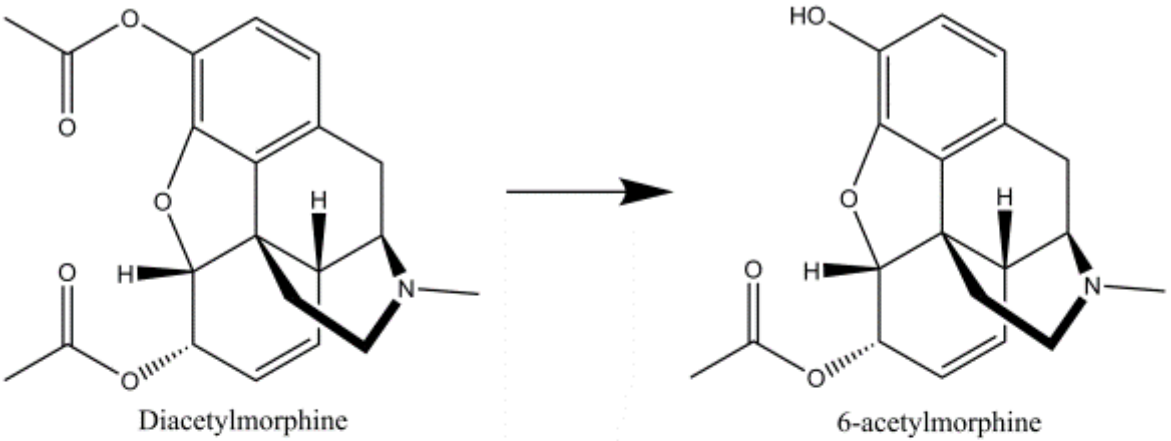


Heroin

"Less addictive"

Ceased production

Made illegal in US in 1924



6-Acetylmorphine

Blood: up to about 2-3 hours

Urine: up to about 18-24 hours

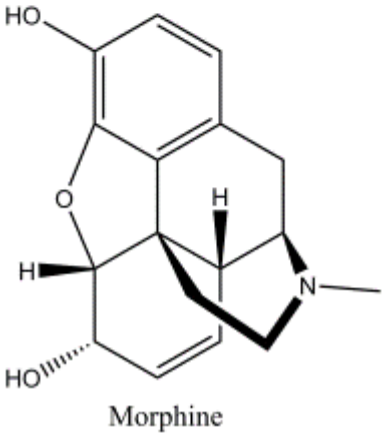
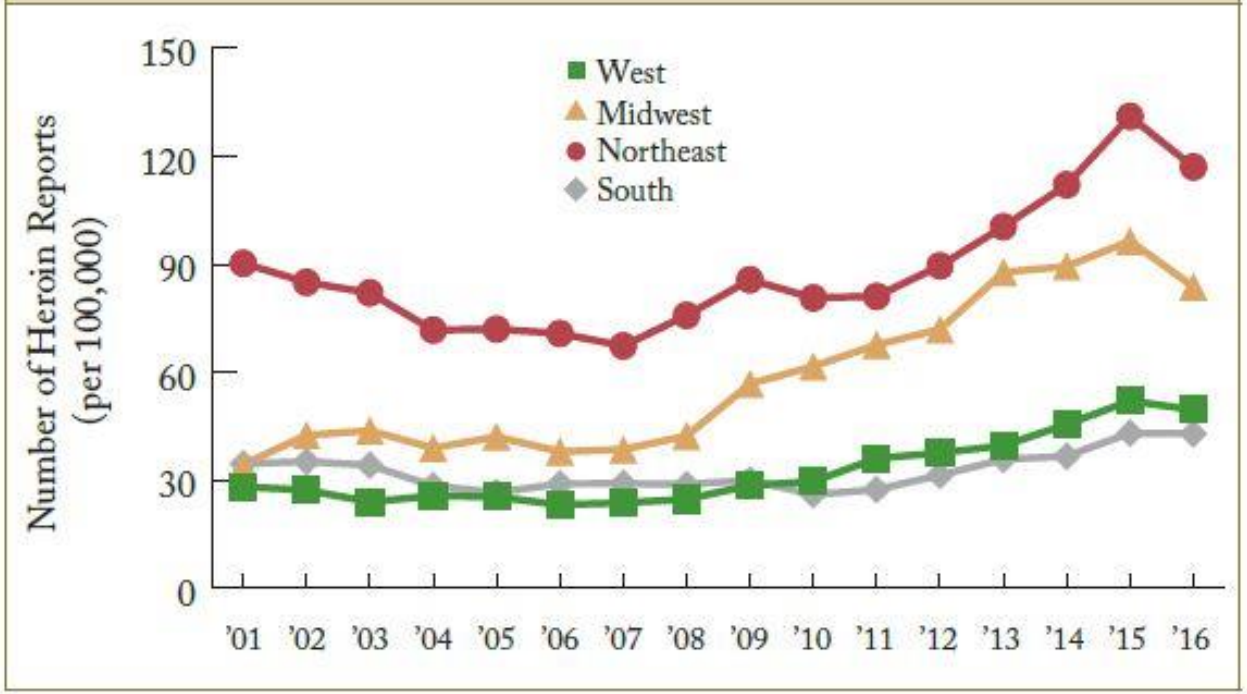


Figure 1.14 Regional trends in heroin reported per 100,000 persons aged 15 or older, January 2001–December 2016

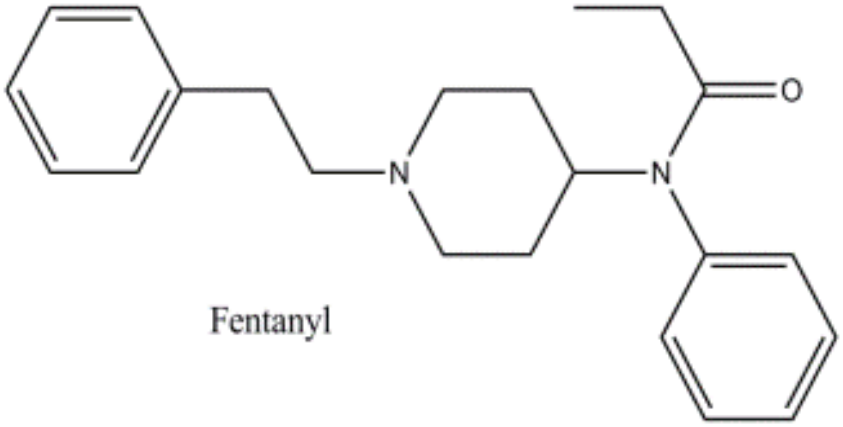


Fentanyl

Jansenn Pharmaceutica

Originally synthesized in 1960

Pharmaceutical drug in 1960s – 2000s



Fentanyl


NDC 50458-036-05 One (100µg/h) System
DURAGESIC® 100µg/h
(FENTANYL TRANSDERMAL SYSTEM)
CII
In vivo delivery of 100µg/h fentanyl for 72 hours
NOT FOR ACUTE OR POSTOPERATIVE USE
Each transdermal system contains:
10 mg fentanyl and 0.4ml alcohol USP
Caution: Federal law prohibits dispensing without prescription.
WARNING: May be habit-forming.
01461014
JANSSEN
PHARMACEUTICA
ATTENTION: Only for use by patient for whom prescribed.
Fentanyl Transdermal Patch
Anonymous Photographer, © 2005 Erowid.org

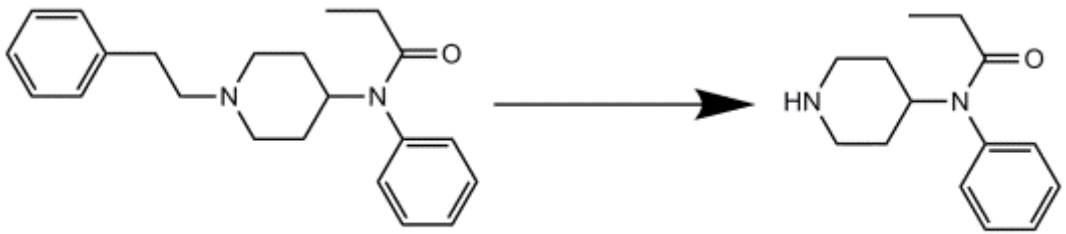

30 Units
Oral Transmucosal
Fentanyl Citrate (OTFC)
CII
equivalent to 400 mcg fentanyl base
Warning: May be habit forming.

Strong mu opioid receptor agonist

Up to about 40 times more potent as heroin

Significant central nervous system effects

- Respiratory depression
- Coma, Death



Fentanyl Norfentanyl

Figure 1.7 Regional trends in fentanyl reported per 100,000 persons aged 15 or older, January 2001–December 2016[1]

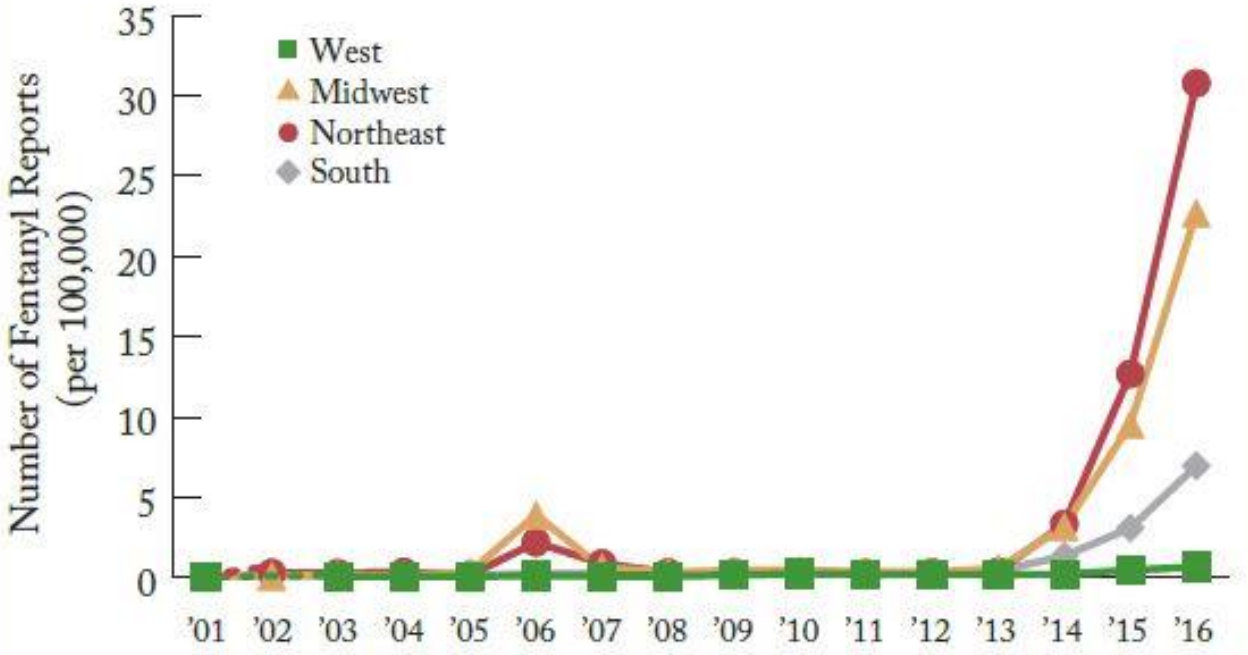


Figure 3.3 Percentage of total drug reports identified as fentanyl, by State, 2012[1]

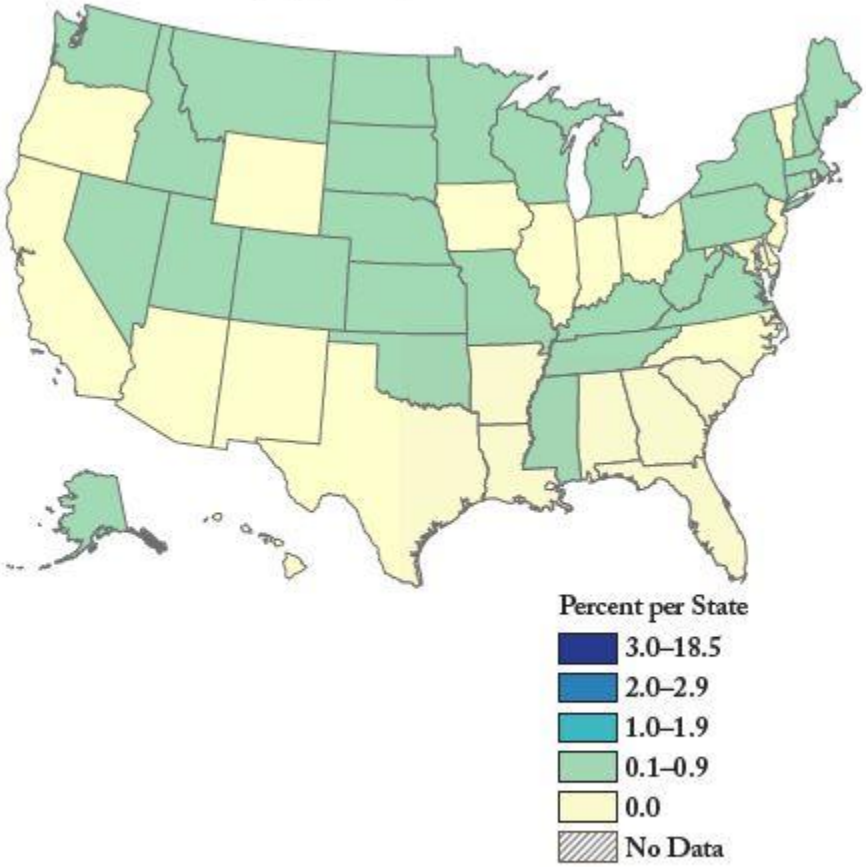
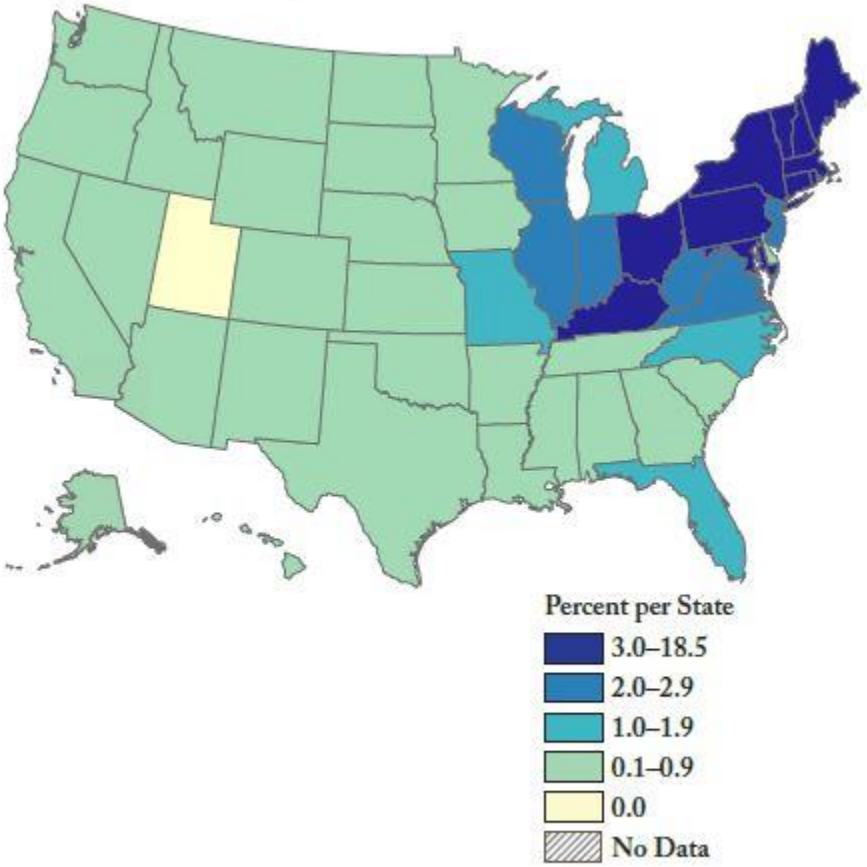


Figure 3.4 Percentage of total drug reports identified as fentanyl, by State, 2016[1]



[1] *Includes drugs submitted to State and local laboratories during the calendar year that were analyzed within three months of the reporting period.*

Fentanyl Analogs

What are they?

A derivative of the drug fentanyl, illicitly produced to circumvent the CSA

(derivative = a chemically engineered modified version of a root substance)

Where do they come from?

Ordered from the "dark web" (Internet sites designed to peddle illicit materials)

Overseas contacts (China is a primary source)

3-methylfentanyl
4-methoxybutyrylfentanyl
2, 3, and 4-fluorobutyrylfentanyl
2, 3, and 4-fluorofentanyl
Acetylfentanyl
Acrylfentanyl
Alphamethylfentanyl
Benzylfentanyl
Betahydroxythiofentanyl
Butyrylfentanyl
Carfentanil
Cyclopentylfentanyl
Cyclopropylfentanyl
Furanylfentanyl
Lofentanyl
N-Methylcarfentanil
Methoxyacetylfentanyl
Ocfentanil
Ohmefentanyl
Parafluoroacrylfentanyl
Remifentanil
Sufentanil
Thienylfentanyl
Thiofentanyl
Trefentanyl
Valerylfentanyl

Many more…

July 2015
Acetylfentanyl

May 2016
Betahydroxythiofentanyl, Butyrylfentanyl

November 2016
Furanylfentanyl, U47700

May 2017
4-Fluoroisobutyrylfentanyl

July 2017
Acrylfentanyl

September 2017
Methoxyacetylfentanyl
Orthofluorofentanyl
Tetrahydrofuranfentanyl

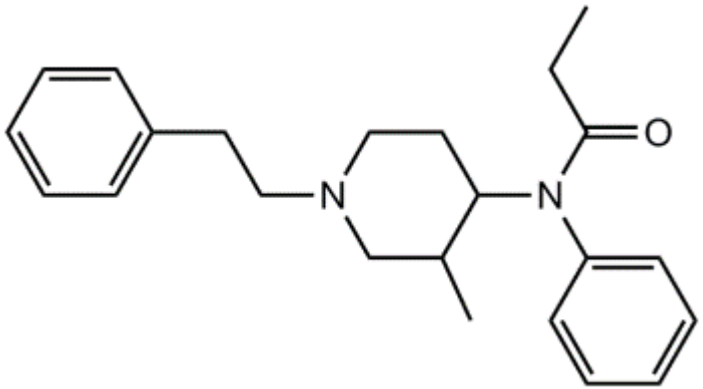
3-methylfentanyl

Synthesized in 1974

Appeared on the illicit drug market in the 1980s

10-15 times more potent than fentanyl

Schedule I in USA



Acetylfentanyl

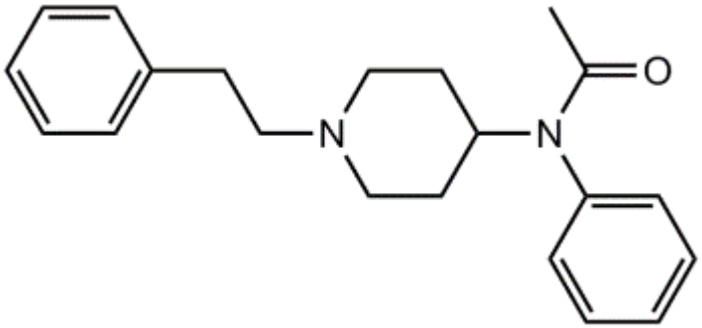
Synthesized in the 1960s

Appeared on the illicit drug market in 2013

Overdoses in Rhode Island and Pennsylvania

Less potent than fentanyl

Schedule I (May 2015)



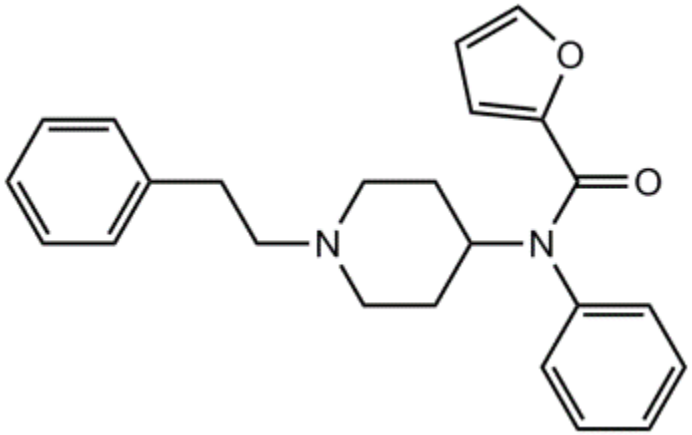
Furanylfentanyl

Synthesized in 1986

Appeared on the illicit drug market in 2015

Similar potency as fentanyl

Schedule I (2016)



Carfentanil

Synthesized in 1974

10,000 times more potent than morphine / 100 times more potent than fentanyl

Marketed as Wildnil (a large animal immobilizer)

Schedule II in the USA

Exposure from veterinary medicine

Chemical warfare implications

Emerged as a unknown contaminant in heroin in 2016

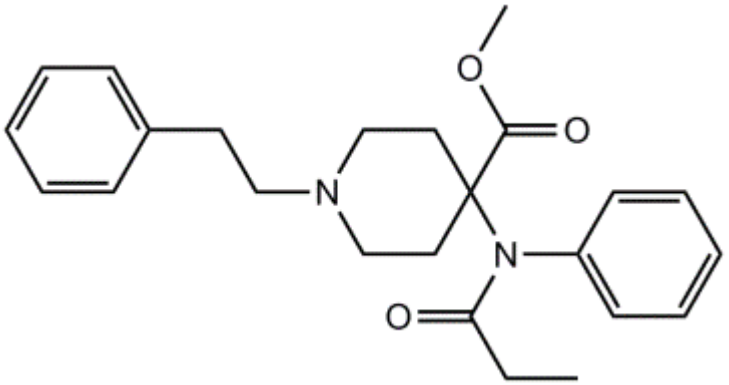
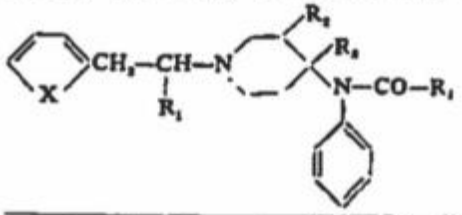


Table 2: Chemical structure, calculated lowest ED_{50} in mg/kg, calculated peak effect and duration of action in hours, relative potency, LD_{50} (mg/kg) and safety margin of N-4-substituted 1-2-arylethyl)-4-piperidinyl-N-phenylpropanamides.



Serial number or generic name	X	R_1	R_2	R_3	R_4	ED_{50} [a]	Peak effect [a]	Duration at n×ED_{50} [b] n = 2	n = 4	n = 8	Relative potency [c]	LD_{50}	Safety margin [d]
R 30 490	—CH=CH—	—H	—H	—CH_2OCH_3	—CH_2CH_3	0.00069	0.15	0.64	1.09	1.61	4 652	10.2	14 783
R 30 730	—S—	—H	—H	—CH_2OCH_3	—CH_2CH_3	0.00071	0.14	0.58	1.00	1.48	4 521	17.9	25 211
★ R 31 833	—CH=CH—	—H	—H	—$COOCH_3$	—CH_2CH_3	0.00032	0.29	1.00	1.55	2.13	10 031	3.39	10 594
R 31 826	—S—	—H	—H	—$COOCH_3$	—CH_2CH_3	0.00037	0.23	0.88	1.40	1.97	8 676	2.80	7 568
R 32 721	—CH=CH—	—CH_3	—H	—$COOCH_3$	—CH_2CH_3	0.00064	0.33	1.20	1.94	2.75	5 016	2.38	3 719
R 32 767	—CH=CH—	—H	—H	—$COOCH_3$		0.00089	0.34	2.99	7.55	>8	3 607	0.16	180
R 32 792	—CH=CH—	—H	—CH_3	—$COOCH_3$	—CH_2CH_3	0.00070	0.55	4.39	>8	>8	4 586	0.20	286
R 32 557	—CH=CH—	—H	—H	—$COCH_3$	—CH_2CH_3	0.00057	0.25	0.84	1.31	1.79	5 632	3.21	5 632
R 33 000	—CH=CH—	—H	—H	—$COCH_3$		0.00070	0.26	0.92	1.46	2.03	4 586	1.38	1 971
R 33 036	—CH=CH—	—H	—H	—$COCH_2CH_3$	—CH_2CH_3	0.0012	0.15	0.64	1.08	1.58	2 675	3.00	2 500
R 33 352	—S—	—H	—H	—$COCH_2CH_3$	—CH_2CH_3	0.00056	0.12	0.42	0.71	1.05	5 732	2.90	5 179
Fentanyl	—CH=CH—	—H	—H	—H	—CH_2CH_3	0.011	0.093	0.51	0.93	1.44	292	3.05	277
R 26 800	—CH=CH—	—H	—CH_3	—H	—CH_2CH_3	0.00058	0.19	1.00	1.80	2.74	5 534	0.96	1 655
Morphine	—	—	—	—	—	3.21	0.31	1.48	2.61	3.94	1	223.0	69.5
Pethidine	—	—	—	—	—	6.04	0.11	0.55	0.92	—	0.531	29.0	4.80

[a]) Calculated by polynomial regression analysis.
[b]) Calculated at the intersection with the polynomial at n × lowest ED_{50}.
[c]) Morphine = 1.
[d]) LD_{50}/lowest ED_{50}.

Janssen, 1976

Animals

How prevalent are they?

7/1/2016 – 9/14/2017

1,911 blood samples tested. 1,039 positive samples. ~54% positivity rate.

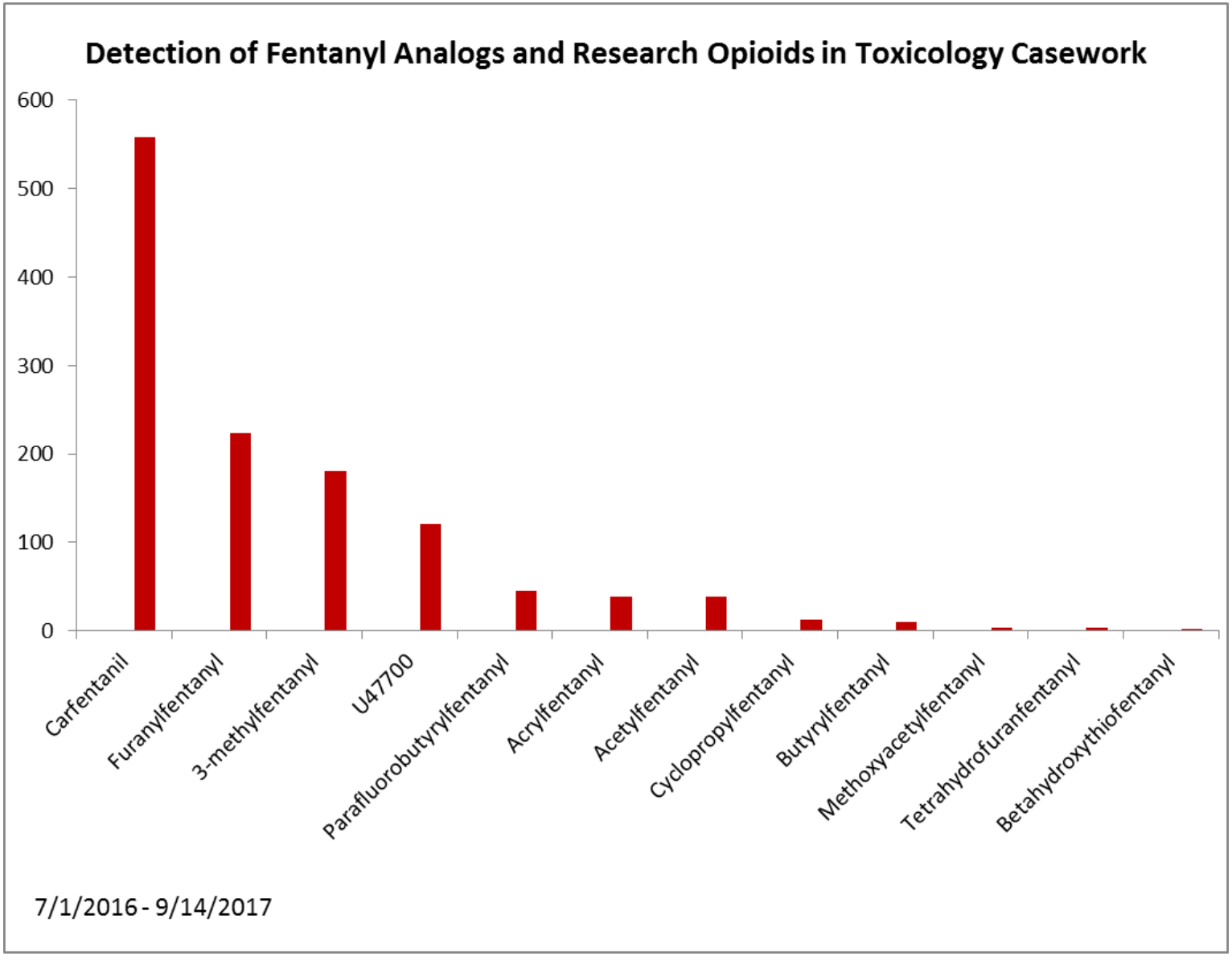
11 different fentanyl analogs/opioids across 26 states

3-methylfentanyl, Acetylfentanyl, Acrylfentanyl, Betahydroxythiofentanyl,

Butyrylfentanyl, Carfentanil, Cyclopropylfentanyl, Furanylfentanyl,

Methoxyacetylfentanyl, Parafluorobutyrylfentanyl, Tetrahydrofuranfentanyl

*Source: Axis Forensic Toxicology internal laboratory data


Detection of Fentanyl Analogs and Research Opioids in Toxicology Casework
600
500
400
300
200
100
0
Carfentanil
Furanylfentanyl
3-methylfentanyl
U47700
Parafluorobutyrylfentanyl
Acrylfentanyl
Acetylfentanyl
Cyclopropylfentanyl
Butyrylfentanyl
Methoxyacetylfentanyl
Tetrahydrofuranfentanyl
Betahydroxythiofentanyl
7/1/2016 - 9/14/2017

Carfentanil

558 positive cases since 7/1/2016 (~29% of all cases)

Mean,183 pg/mL

Median, 100 pg/mL

90% Percentile, 403 pg/mL

10.0 – 2,732 pg/mL

Potent substance

Purity of product used?

Case Studies

26 year old female

Was seen using heroin

Found deceased the next morning

Iliac Blood

- THC-COOH (10.1 ng/mL)
- Topiramate (7.5 mcg/mL)
- Carfentanil (234 pg/mL)

Urine

- THC-COOH (204 ng/mL)
- Buprenorphine (4 ng/mL)
- Norbuprenorphine (20 ng/mL)
- Norfentanyl (0.5 ng/mL)
- Morphine (58 ng/mL)
- Carfentanil (Qualitative)

33 year old female

Found deceased on bathroom floor

Narcan kit found – dose used

Femoral Blood

- Morphine (10.9 ng/mL)
- THC (2.7 ng/mL)
- THC-COOH (29.0 ng/mL)
- Carfentanil (145 pg/mL)

Urine

- THC-COOH
- Morphine
- Codeine

When should a toxicologist, or pathologist consider fentanyl or fentanyl analogs?

History consistent with opioid overdose

Negative routine toxicology

Use information from scene evidence!

Increases in Fentanyl-Related Overdose Deaths — Florida and Ohio, 2013–2015

Weekly / August 26, 2016 / 65(33);844–849

Notes from the Field: Furanyl-Fentanyl Overdose Events Caused by Smoking Contaminated Crack Cocaine — British Columbia, Canada, July 15–18, 2016

Weekly / September 23, 2016 / 65(37);1015–1016

Opioid Overdose Outbreak — West Virginia, August 2016

Weekly / September 22, 2017 / 66(37);975–980

Overdose Deaths Related to Fentanyl and Its Analogs — Ohio, January–February 2017

Weekly / September 1, 2017 / 66(34);904–908

Deaths Involving Fentanyl, Fentanyl Analogs, and U-47700 — 10 States, July–December 2016

Weekly / November 3, 2017 / 66(43);1197–1202

What to expect in the future?

More of the same…the cat and mouse games will continue…

Thank you!

kshanks@axisfortox.com

Heroin was originally marketed as a pharmaceutical drug by what company?

Fentanyl is typically prescribed to patients in what form?

What veterinary medication has been found in street heroin in the USA starting in 2016?