PainWeek®

Will the REAL Fentanyl Please Stand Up?

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- Consulting Fee (e.g., Advisory Board): Purdue Pharma LP

Disclosure Dr. Bettinger

- Consulting Fee (e.g., Advisory Board): Hisamitsu America, Inc., PainScript Corporation

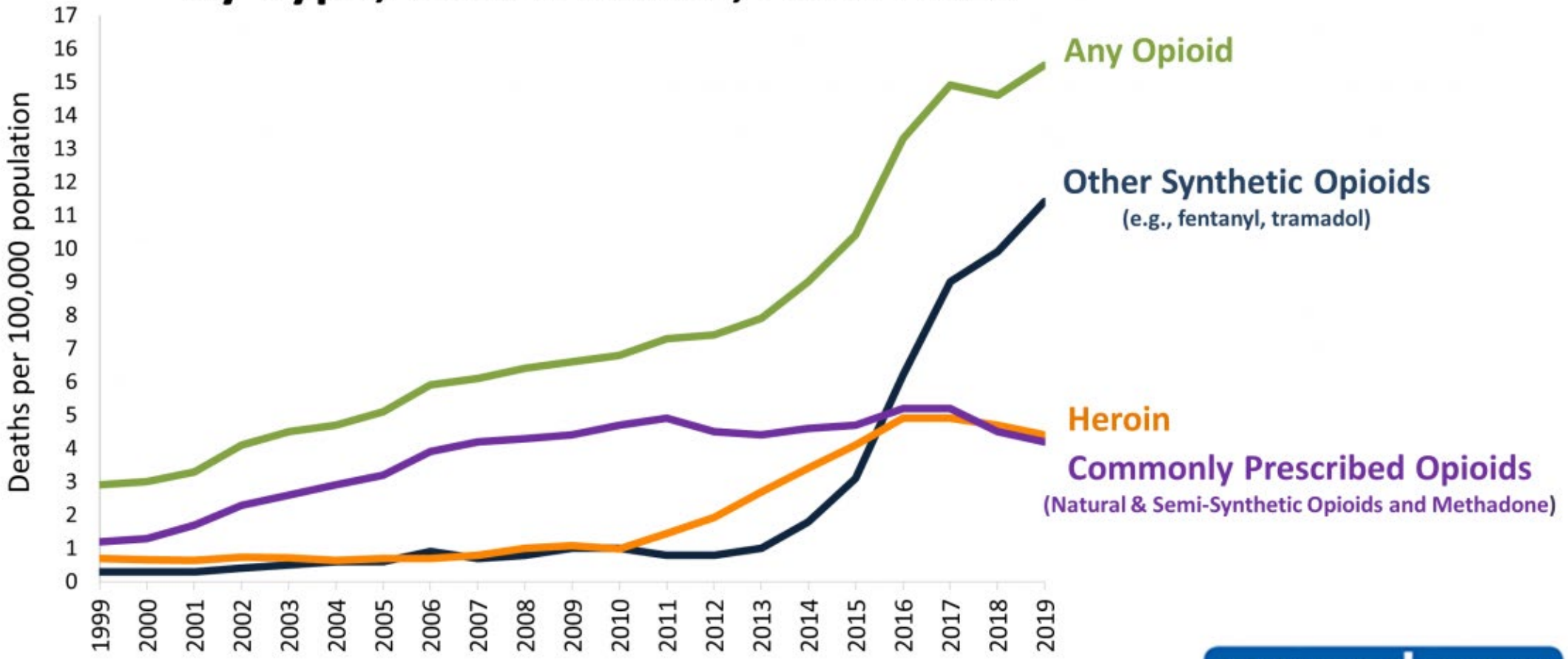
Learning Objectives

- Recognize the multitude of factors responsible for the opioid overdose death rates across the United States, emphasizing the role of fentanyl analogues

- Delineate between various pharmaceutical and illicitly manufactured fentanyl compounds by physiochemical, pharmacodynamic, and pharmacokinetic characteristics that helps debunk common myths and mischaracterizations about this crisis

- Identify clinical situations in which higher dose naloxone products may be needed in the reversing overdoses involving fentanyl analogues

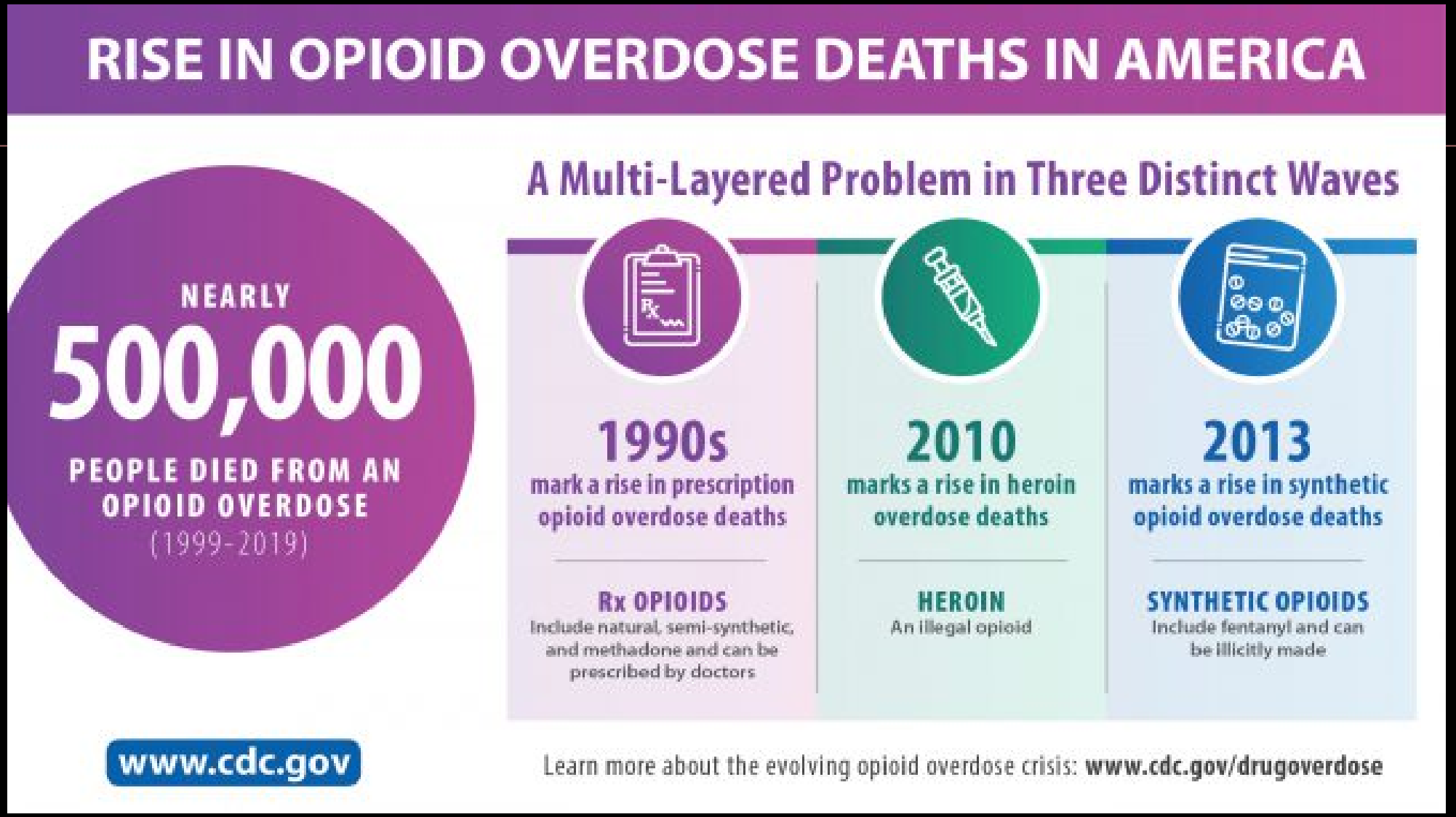
Overdose Death Rates Involving Opioids, by Type, United States, 1999-2019



SOURCE: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2020. https://wonder.cdc.gov/.

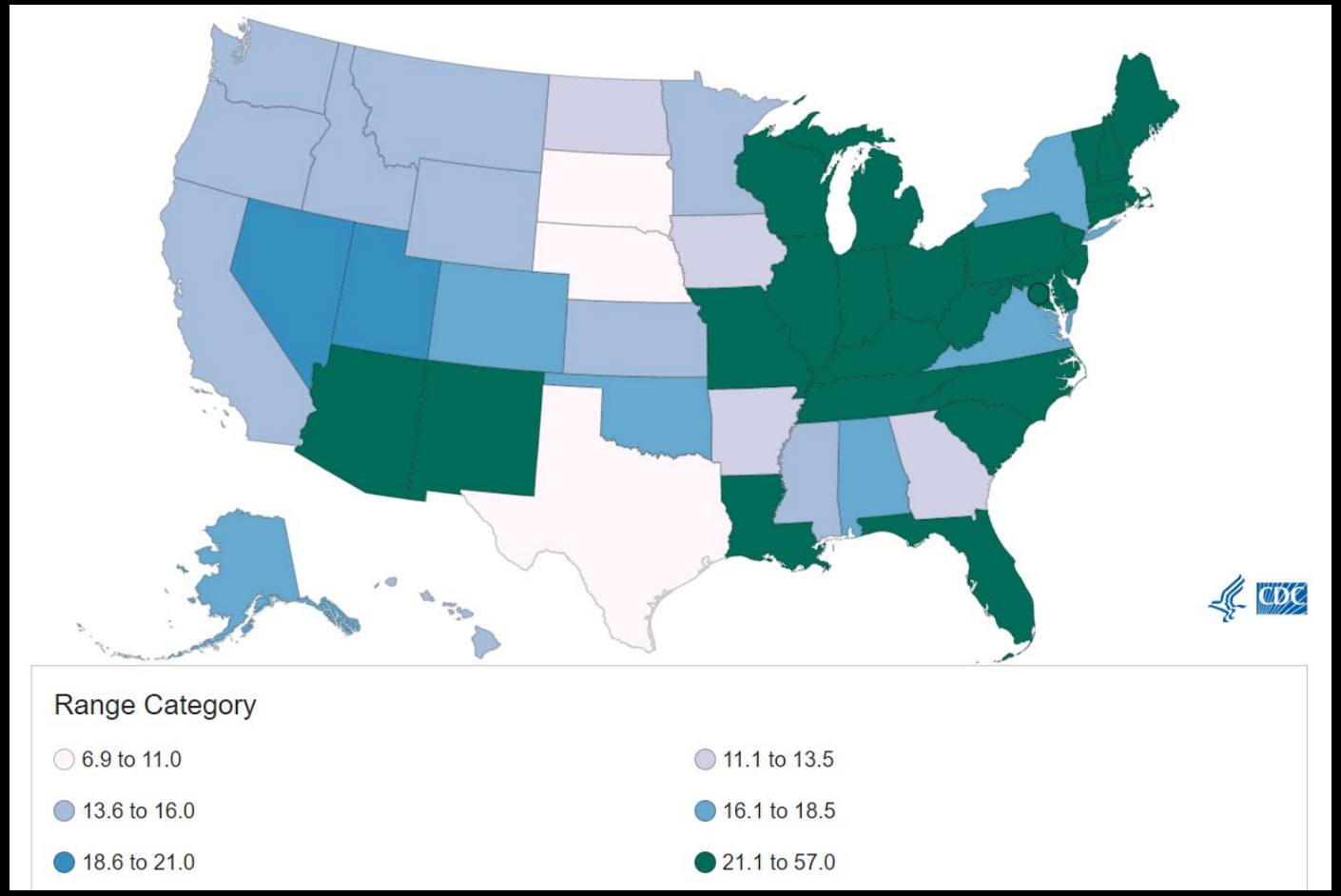
www.cdc.gov
Your Source for Credible Health Information

https://www.cdc.gov/drugoverdose/images/overdose-death-rates-2019-large.png?noicon



https://www.cdc.gov/drugoverdose/images/3-waves-inforaphic-medium.jpg?noicon

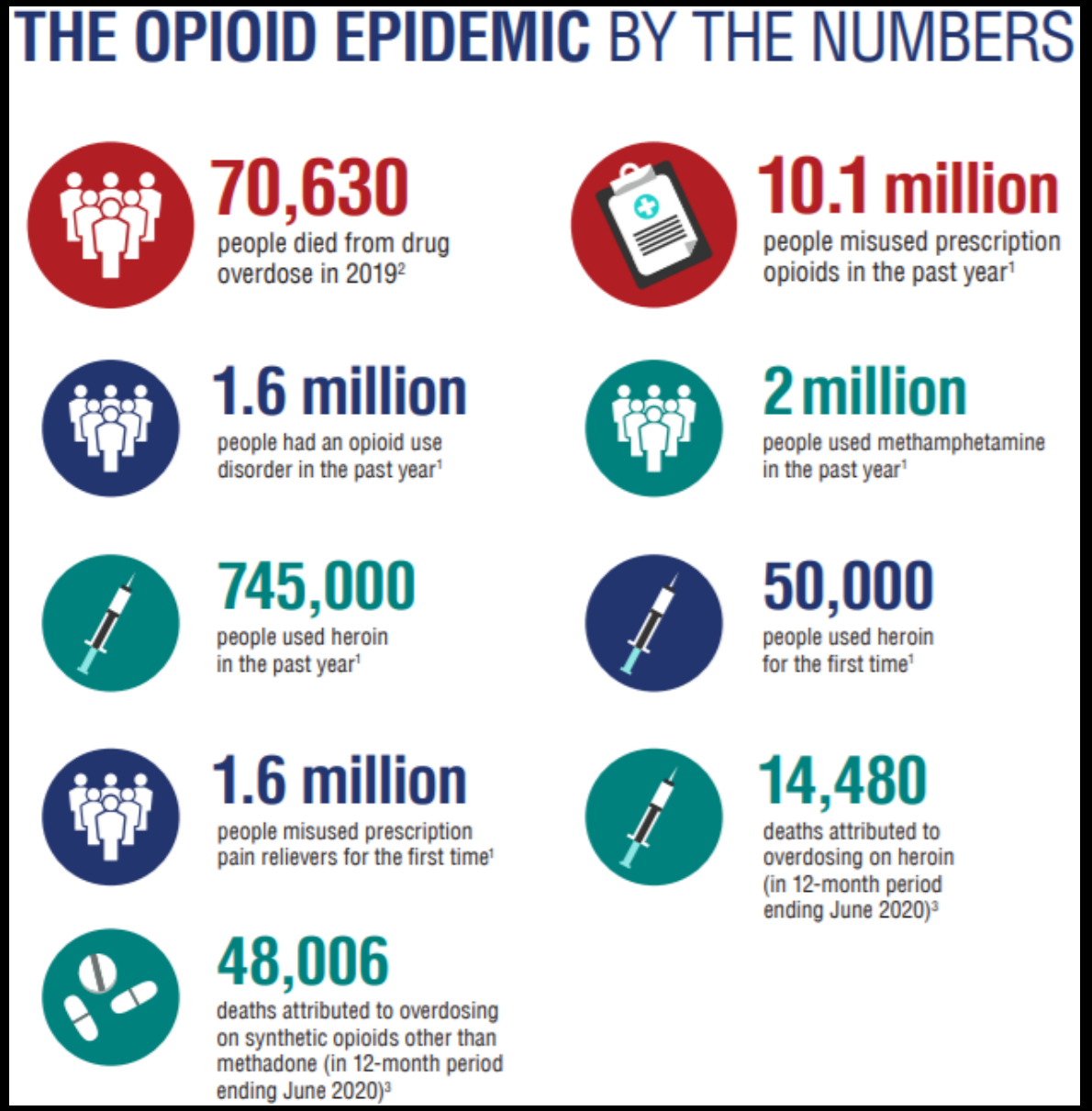
Number and Age-adjusted Rates of Drug Overdose 2019



State	Deaths
West Virginia	870 (52.8)
Ohio	4251 (38.3)
Pennsylvania	4377 (35.6)
Florida	5268 (25.5)
New York	3617 (18.2)
California	6198 (15)
Tennessee	2089 (31.2)
Texas	3136 (10.8)

- Rates are age-adjusted per 100,000 population, US Census 2000.

https://www.cdc.gov/drugoverdose/data/statedeaths/drug-overdose-death-2019.html



https://www.hhs.gov/opioids/sites/default/files/2021-02/opioids-infographic.pdf

Drug Overdose Data

2019

- 70,630 drug overdose deaths
  - 4% increase from 2018
- 49,860 overdose deaths involved opioids
  - 70.6% of all drug overdoses
- 36,000 overdose deaths involved synthetic opioids (other than methadone)
  - 73% of opioid-involved deaths
  - 15% increase from 2018
- 14,000 overdose deaths involved heroin
  - 28% of opioid-involved deaths
- Prescription opioid overdoses not disclosed
  - CDC instead reports total prescription opioid overdoses since 1999

2020

- 90,722 drug overdose deaths
  - 28.9% increase from 2019
- 67,574 overdose deaths involved opioids
  - X% of all drug overdoses
- 55,363 overdose deaths involved synthetic opioids (other than methadone)
  - 73% of opioid-involved deaths
  - 15% increase from 2018
- 13,444 overdose deaths involved heroin
  - 28% of opioid-involved deaths
- 13,383 Natural & semi-synthetic opioids
  - Heroin is a natural opioid

https://www.cdc.gov/drugoverdose/data/index.html
https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm#notes

CDC Centers for Disease Control and Prevention
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A-Z Index

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Opioid Overdose

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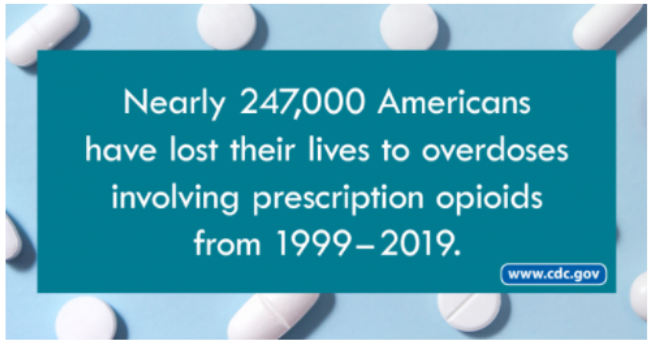
Overview

Millions of Americans suffer from pain and are often prescribed opioids to treat their conditions. However, the dangers of prescription misuse, opioid use disorder, and overdose have been a growing problem throughout the United States.



Since the 1990s, when the amount of opioids prescribed to patients began to grow, the number of overdoses and deaths from prescription opioids has also increased. Even as the amount of opioids prescribed and sold for pain has increased, the amount of pain that Americans report has not similarly changed.

From 1999 to 2019, nearly 247,000 people died in the United States from overdoses involving prescription opioids. Overdose deaths involving prescription opioids more than quadrupled from 1999 to 2019[1].

References

1. Wide-ranging online data for epidemiologic research (WONDER). Atlanta, GA: CDC, National Center for Health Statistics; 2020. Available at http://wonder.cdc.gov.

https://www.cdc.gov/drugoverdose/data/prescribing/overview.html

Polysubstance Overdose Deaths Are the True Focus of Today's Opioid Crisis

- Just Opioids?
  - In 2016, 80% of synthetic opioid overdose deaths involved other drugs
    - Rx Opioids (23.7%)
    - Heroin (37.4%)
    - Cocaine (40.3%)
- Cocaine involved in 19,502 drug overdose deaths in 2020
  - 6,720 in 2015
  - 290% increase
- Psychostimulants with abuse potential involved in 23,283 in 2020
  - 5,689 in 2015
  - 409% increase

https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm#notes
https://www.cdc.gov/drugoverdose/data/otherdrugs.html#polysubstance

Expansion of Illicitly Manufactured Fentanyl & Fentanyl Analogs

- Illicitly manufactured fentanyl and fentanyl analogs
  - Counterfeit pills, heroin, cocaine, and methamphetamine
- Fentanyl is a deadly additive to non-opioid drugs
- In a 10 state study, 57% of overdose deaths tested positive
  - Fentanyl
  - Fentanyl analogs (20%)
    - Carfentanil (11%)
  - Also tested positive for cocaine, methamphetamine, or heroin

- Detection of fentanyl analogs requires specialized toxicology testing
  - Not routinely detected
  - Underreported

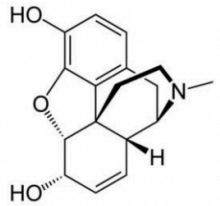
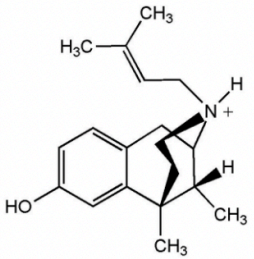
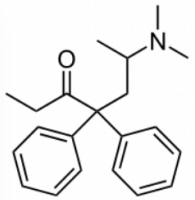
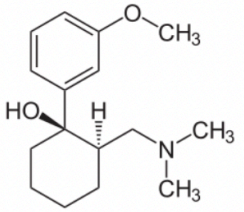
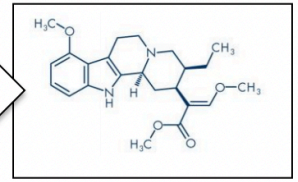
https://www.cdc.gov/drugoverdose/data/synthetic/index.html
https://www.cdc.gov/drugoverdose/data/otherdrugs.html#polysubstance

One of these Fentanyls is NOT Like the Other

Pharmaceutical vs Illicit Fentanyl Products

Pharmaceutical Products	Illicit Fentalogues
Fentanyl	Acryloyl (acryl) fentanyl
Sufentanil	Methyl fentanyl derivatives
Alfentanil	Ocfentanil
Remifentanil	Butyrl fentanyl
Carfentanil (animal use)	AND MANY, MANY MORE

Base Chemical Structure of Fentanyl and its Derivatives

PHENANTHRENES	BENZOMORPHANS	PHENYLPIPERIDINES	DIPHENYLHEPTANES	PHENYLPROPYL AMINES
				
MORPHINE	PENTAZOCINE	FENTANYL	METHADONE	TRAMADOL
Buprenorphine* Butorphanol* Codeine Dextromethorphan* Dihydrocodeine Heroin (diacetyl-morphine) Hydrocodone* Hydromorphone* Levorphanol* Methylnaltrexone** Morphine (Opium, conc) Nalbuphine* Naloxone* Naloxegol* Naltrexone** Oxycodone* Oxymorphone*	Pentazocine	Alfentanil Fentanyl Remifentanil Sufentanil Meperidine Diphenoxylate[a] Loperamide[a] **Fentalogues** **Illicit Fentanyl Analogues** Furanyl fentanyl Acetyl fentanyl Fluoro-fentanyl Carfentanil Others[b]	Methadone Propoxyphene **Mitragynine (Kratom)**	Tapentadol Tramadol 
CROSS-SENSITIVITY RISK				
PROBABLE	POSSIBLE	LOW RISK	LOW RISK	LOW RISK

*Agents lacking the 6-OH group of morphine, possibly decreases cross-tolerability within the phenanthrene group
**6-position is substituted with a ketone group and tolerability is similar to hydroxylation

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Fentanyl

- First synthesized by Dr. Paul Janssen in 1960
- First approved by FDA in 1968
  - Only in combination with droperidol (50:1 ratio… Innovar) → Abuse Deterrent Tech??
- Finally approved as stand-alone product in 1971
- Became increasingly popular as an anesthetic throughout 1970s and into the 80s
  - One of the sparks of opioid drug delivery development and other fentanyl-like compounds

Stanley TH, Egan TD, Van Aken H: A tribute to Paul A. J. Janssen: Entrepreneur extraordinaire, innovative scientist, and significant contributor to anesthesiology. Anesth Analg 106:451-462, 2008.
Stanley TH. The fentanyl story. J Pain. 2014;15(12):1215-26

Now, How Many Products are There?

Fentanyl Product	Route of Administration
Fentanyl Citrate Injection	Intravenous Intramuscular
Transdermal Fentanyl	Transdermal
Transmucosal Immediate-Release Fentanyls (TIRFs)	Buccal • Tablet: Fentanyl citrate • Film: Fentanyl citrate Lozenge: Fentanyl citrate ('lollipop') Nasal Spray: Fentanyl citrate Sublingual • Tablet: Fentanyl citrate • Spray: Free fentanyl

Bettinger JJ, Fudin J, Schatman M, et al. Fentanyl: Separating fact from fiction. Practical Pain Management. 2018;18(6):59-67

	Route of Administration:	Bioavailability	Protein Binding	Terminal Half-Life
Transdermal Fentanyl	Transdermal	92%	80-85%	20-27 hours after patch removal
Fentanyl Citrate Injection	IV or IM	100%	80-85%	2-4 hours
TIRFs	Buccal • Tablet • Film Lozenge Nasal Spray Sublingual • Tablet • Spray	Buccal • Tablet – 65% • Film – 71% Lozenge – 50% Nasal Spray – 89% Sublingual • Tablet – 54% • Spray – 76%	80-85%	Buccal • Tablet – 2.6 to 11.7 hr • Film – ~14 hr Lozenge – ~7 hr Nasal Spray – 15 to 25 hr Sublingual • Tablet – 5-14 hr • Spray – 5-12 hr

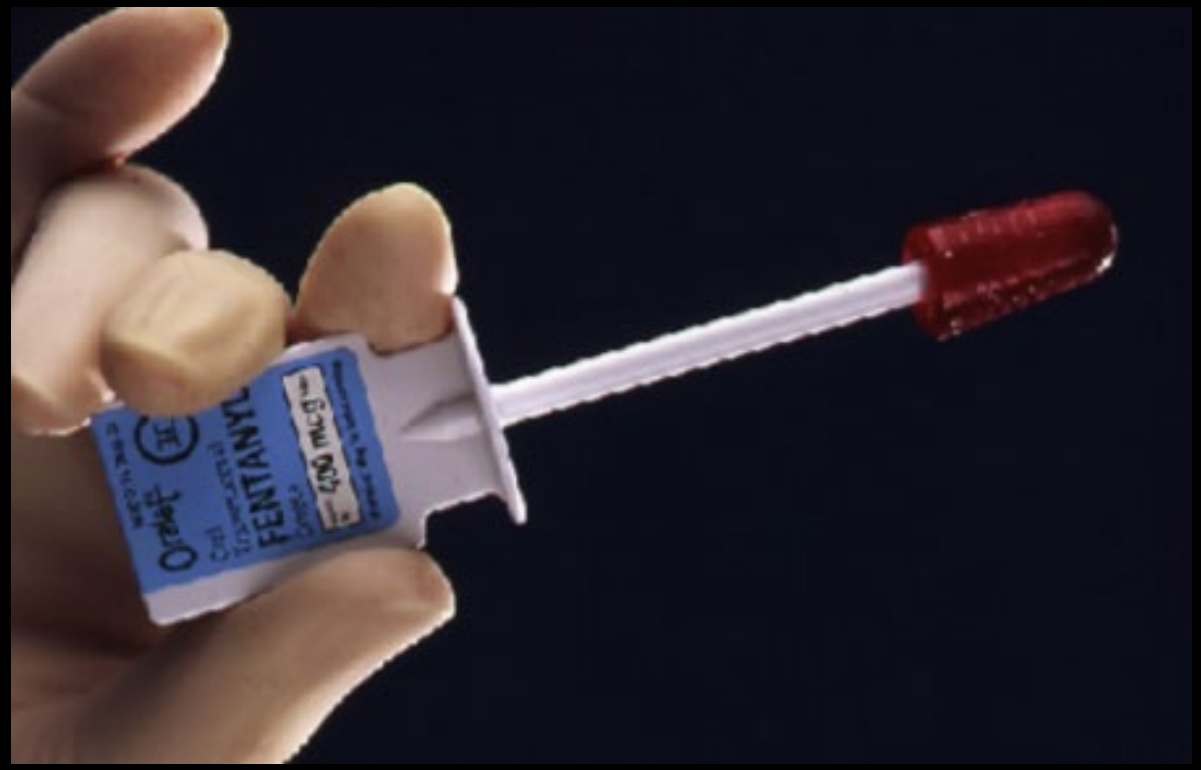
Bettinger JJ, Fudin J, Schatman M, et al. Fentanyl: Separating fact from fiction. Practical Pain Management. 2018;18(6):59-67

What about those TIRFs??

- The original intent around TIRFs was that their simple and non-invasive utility allowed patients, especially children, to be easily and safely titrated prior to surgery
  - When desired effect was met, the drug could be removed
- Oralet, lozenge on a stick, was first TIRF approved in 1993 for specific use as a premedication prior to surgery in adults and children
  - Hospital/supervised use only
- Very soon after its approval, pain physicians began studying its utility in treating breakthrough pain, particularly in those with cancer
  - Again, immediate effects were beneficial to reduce breakthrough pain
- Wasn't until 1998 that Actiq was approved specifically for opioid-tolerant patients having breakthrough cancer pain

Stanley TH, Egan TD, Van Aken H: A tribute to Paul A. J. Janssen: Entrepreneur extraordinaire, innovative scientist, and significant contributor to anesthesiology. Anesth Analg 106:451-462, 2008.
Stanley TH. The fentanyl story. J Pain. 2014;15(12):1215-26

Oralet vs Actiq



https://www.jpain.org/action/showPdf?pii=S1526-5900%2814%2900905-5

TIRFs Continued

- Since that time, several additional TIRFs have been developed and approved by the FDA
    - Many of these have optimized delivery, improved bioavailability and shortened onset of action
- Simultaneously, increasing rates of TIRF misuse and inappropriate prescribing were seen throughout the following decades

TIRFs REMS Program

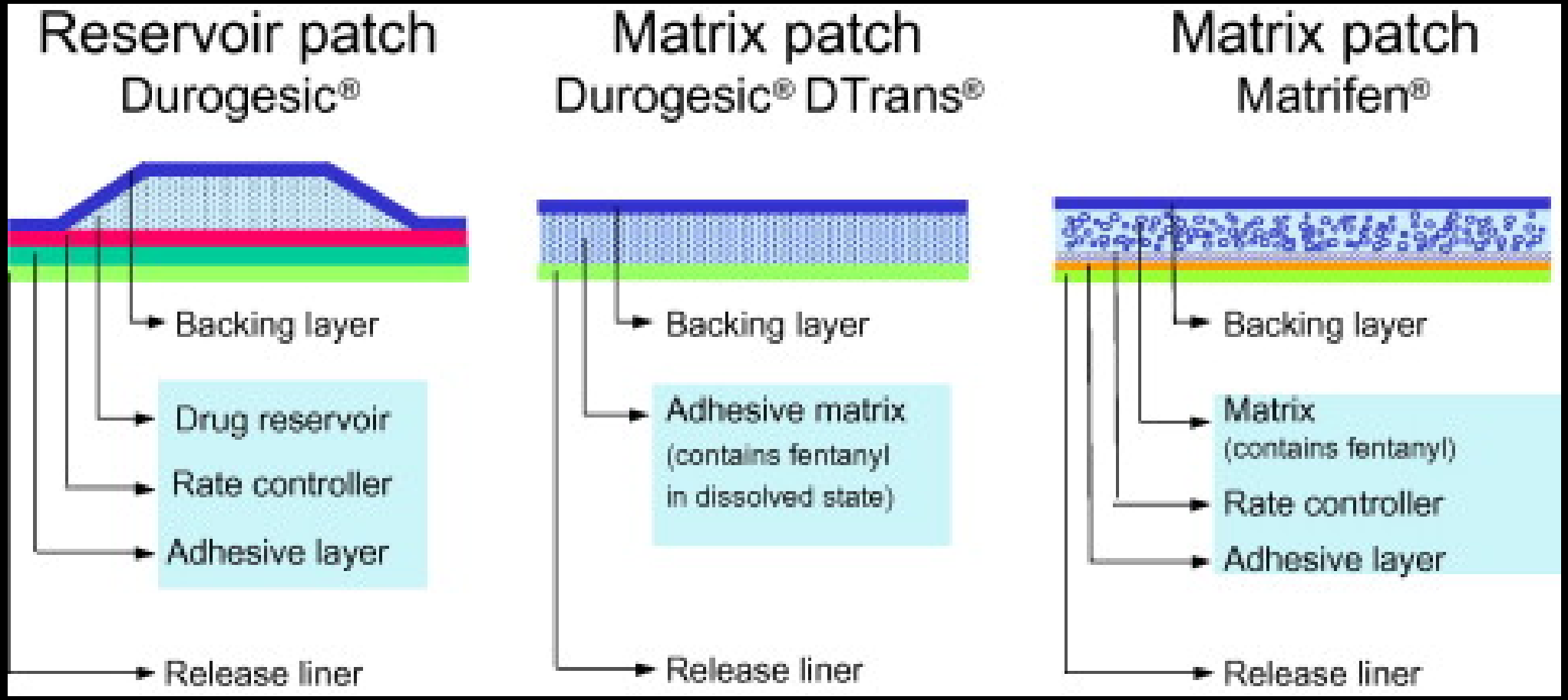
- Starting in 2011, FDA has implemented a REMS for all TIRFs products shared by all companies

- Originally included:
  - Restricted distribution program
  - Providers and pharmacies must be certified
  - Patients required to sign patient-provider agreement form

- December, 2020: Modified REMS was approved
  - Added requirement of documentation of opioid tolerance with every TIRF Rx
  - Pharmacies must assess for a change in patients' opioid tolerance
  - Patients using TIRF outpatient must be enrolled in a registry

Transmucosal immediate-release fentanyl (TIRF) Medicines. FDA. 2020. Available: https://www.fda.gov/drugs/information-drug-class/transmucosal-immediate-release-fentanyl-tirf-medicines

The Evolution of the Patch



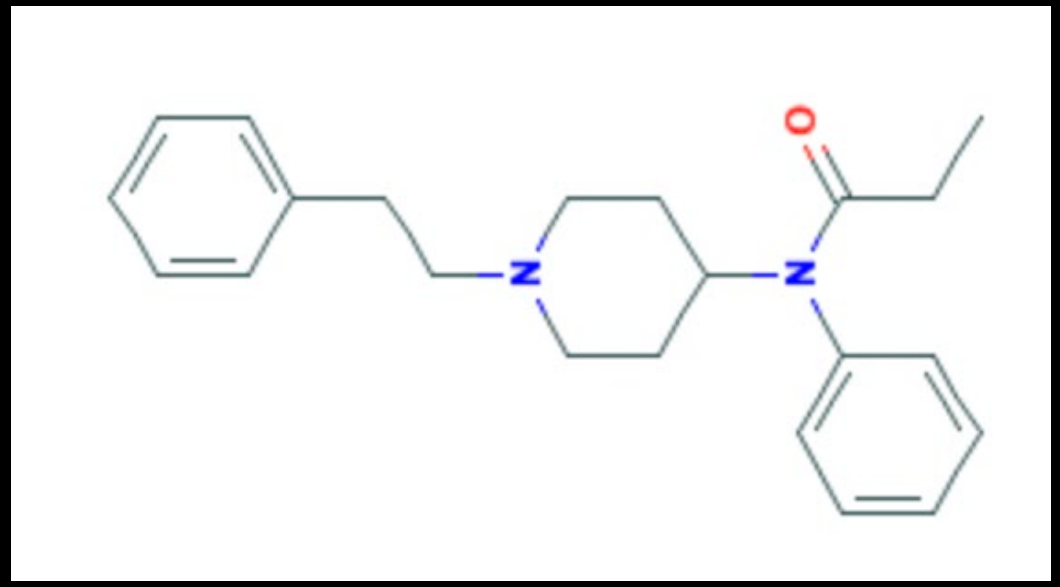
https://www.sciencedirect.com/science/article/abs/pii/S0939641110000354

Sufentanil

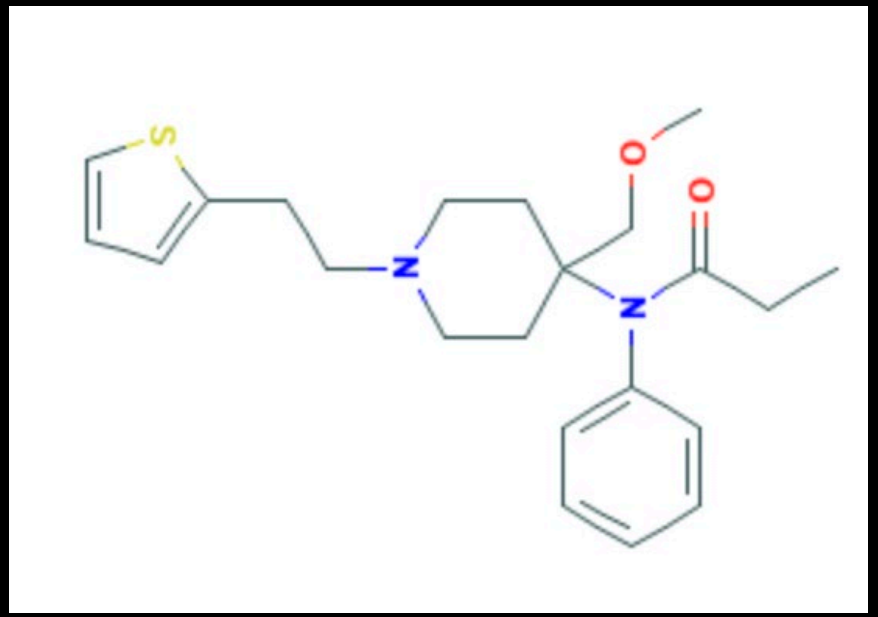
- First synthesized by Dr. Janssen in 1974
- IV formulation approved in 1984 for induction of anesthesia
  - Later approved for epidural delivery in combination with bupivacaine
- Approved as sublingual formulation in November 2018
  - Use for acute pain I medically supervised settings

Stanley TH, Egan TD, Aken HV. A tribute to Dr. Paul A. J. Janssen: entrepreneur extraordinaire, innovative scientist, and significant contributor to anesthesiology. Anesth. Analg. 2008;106(2):451-62

Comparison of Chemical Structures



Fentanyl



Sufentanil

Images obtained from Pubchem. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Fentanyl
https://pubchem.ncbi.nlm.nih.gov/compound/Sufentanil#section=2D-Structure

Physiochemical Characteristics

Opioid:	Binding affinity (Ki value, nM)[1]	Partition Coefficient (Log P)[a]	Molecular Weight (Da)[2]	Equivalent Equianalgesic IM dose (mg)[b]
Sufentanil	0.1380	3.95	386	~500-1000 times more potent
Buprenorphine	0.2157	4.98	468	~40 times more potent[c]
Hydromorphone	0.3654	1.84	285	1.5
Oxymorphone	0.4055	0.83	301	1
Levorphanol	0.4194	3.1[4]	257[4]	2
Morphine	1.168	0.76	285	10
Fentanyl	1.346	4.05	336	0.1 – 0.2
Oxycodone	25.87	0.82	315	20
Codeine	734.2	1.14	299	130

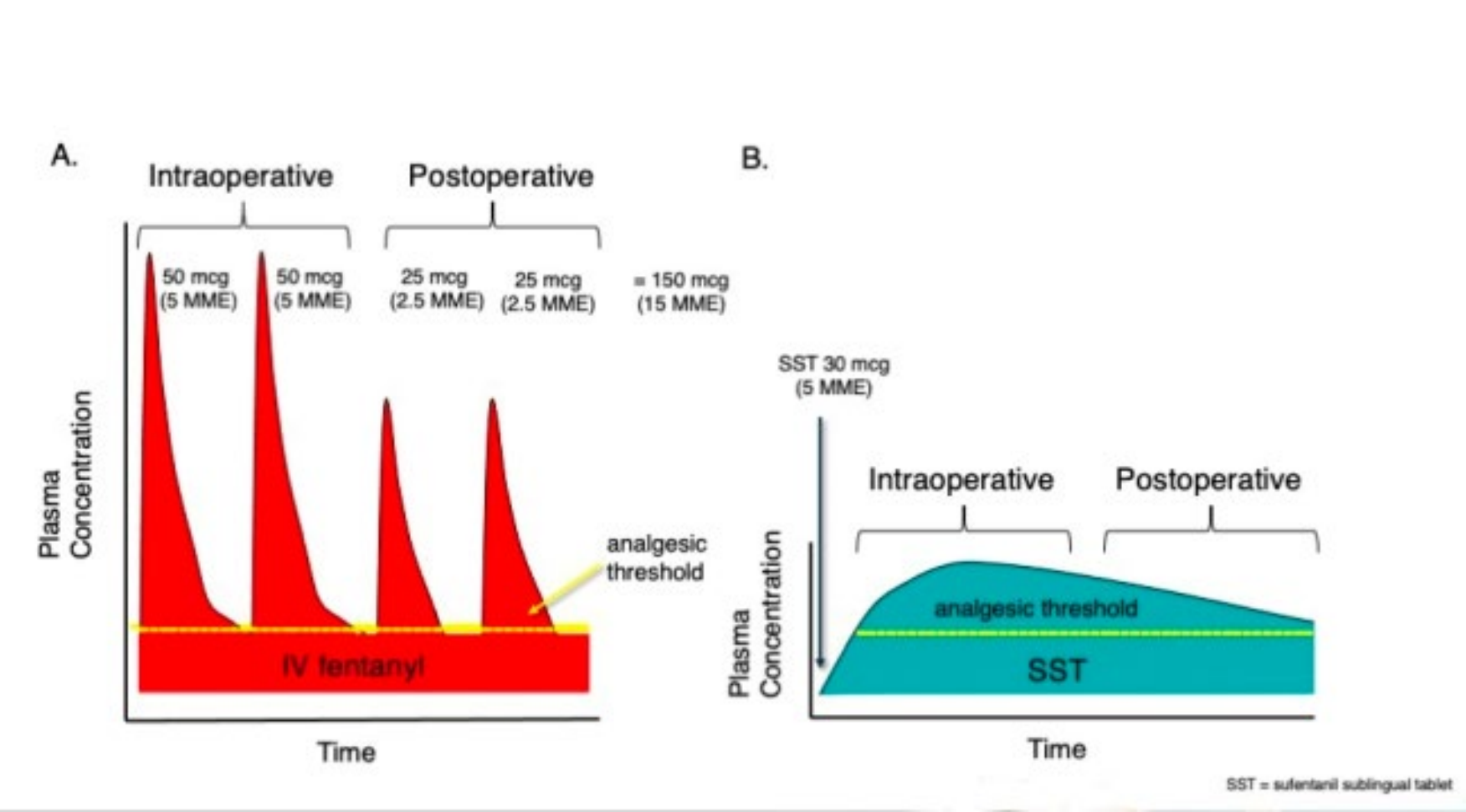
[a]Log P corresponds to the logarithm of the ratio of the concentrations of the studied compound in octanol and in water: LogP = Log (C_{oct}/C_{water}).
[b]For Equianalgesic IM doses, time of peak analgesia in non-tolerant patients ranges from one-half to one hour and the duration of four to six hours. Doses are expressed in milligram strength.
[c]Potency when calculated for buprenorphine is relative, given it has different pharmacologic effects on opioid receptors than traditional opioid agonist medications.

Pharmacokinetic Characteristics of Sublingual Sufentanil

- Sublingual tablet dissolves within 5 minutes while it deposits into the sublingual mucosa
- Forms a sublingual tissue depot which allows for a slower overall absorption such that peak plasma concentrations are much lower (17-fold) compared to IV dosing
- Onset of action occurs within 15 minutes and duration of analgesia of approximately 3-4 hours

Fisher DM, et al. Anesthesiology. 2018;128(5):943-952.

So, If More Potent, More Dangerous?

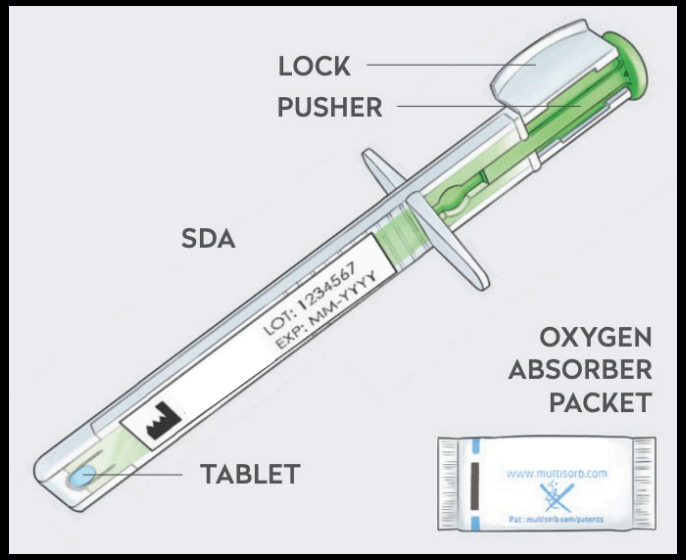


Fudin J, Bettinger JJ, Dasta JF. A commentary on opioid stewardship: Fentanyl, sufentanil, and perioperative pain. Practical Pain Management. 2020;20(6).

Well, What About its Availability?

- Of course, IV and epidural formulations are medically supervised settings only

- This is also true for sublingual sufentanil
  - Only indicated and can be used in medically supervised settings



https://www.dsuvia.com/pdf/DSUVIADirectionsForUse.pdf

Overall Safety Population: Typical Opioid Adverse Events

Adverse Events	SST 30 mcg,[1] N=323	Placebo,[2] N=54
Patients with ≥1 Adverse Event	32.5%	38.9%
Nausea	22.9%	22.2%
Headache	5.3%	11.1%
Dizziness	4.0%	3.7%
Vomiting	3.1%	1.9%
Pruritis	1.9%	3.7%
Hypotension	1.9%	3.7%
Somnolence	1.5%	3.7%
Confusional state	0.3%	0
Constipation	0.3%	0

Miner JR, et al. *Pain Management*. 2019;9(3):259-271. 2. Minkowitz HS, et al. *Pain Pract*. 2017;17(7):848-858.

But, the Peri-Operative Goal is to be Opioid Free?

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Research Article

DOI: 10.36959/377/341

Reduced Opioid Use and Reduced Time in the Postanesthesia Care Unit Following Preoperative Administration of Sublingual Sufentanil in an Ambulatory Surgery Setting

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[2]*United Health Services, Johnson City, NY, USA*

Abstract

Background: As the number of surgeries performed in an outpatient setting continues to rise, it is important to continually optimize perioperative pain management to enhance patient outcomes and optimize efficiency of the postanesthesia care unit (PACU). While intravenous (IV) fentanyl is commonly used to provide pain relief both intra- and postoperatively, IV bolus dosing can have negative hemodynamic effects during surgery and induce nausea and vomiting in the PACU. In this study, we evaluated whether preoperative administration of a sublingual sufentanil tablet, a novel analgesic with unique pharmacokinetic characteristics, could reduce overall opioid use and time in the PACU.

Methods: In this prospective medication use evaluation study, a single sublingual sufentanil tablet (SST) 30 mcg was administered prior to surgery in patients undergoing an outpatient procedure. Perioperative opioid use, vasopressor use, and time in the PACU were compared with historical (non-SST-treated) controls.

Results: A total of 127 patients were evaluated with nearly identical baseline demographics. Significantly fewer SST-treated patients required intraoperative IV opioid following dosing with SST compared with the control group (61.7% vs. 97.5%, respectively; $p < 0.001$). SST patients received a total preoperative and intraoperative mean opioid dose of 10.9 mg milligram morphine equivalents (MME), while the mean dose for controls was 20.0 mg MME ($p < 0.001$). Fewer SST-treated patients required any postoperative opioid (10.5% vs. 63.0%; $p < 0.001$) with overall opioid utilization being reduced by over 50% with SST use throughout the perioperative setting (11.8 MME vs. 24.6 MME; $p < 0.001$). Finally, significantly fewer patients in the SST group received adrenergic agonists during surgery and discharge from the PACU occurred 34% faster than controls (36.3 min vs. 54.9 min; $p < 0.001$).

Conclusion: Preoperative administration of SST results in significant reductions in opioid use during outpatient surgery and facilitates shorter PACU stays.

Results

	Control (n = 80)	SST (n = 47)	P-value:
Preoperative and Intraoperative Opioid Use			
Patients Receiving Intraoperative IV Opioids	97.5%	61.7%	P < 0.001
Pre- and Intraoperative Total Opioid Dose (MME; Mean ± SEM)	20.0 ± 1.3 mg	10.9 ± 1.0 mg	P < 0.001
Postoperative Opioid Use			
Patients Requiring Postoperative Opioids	63.0%	10.6%	P < 0.001
Postoperative Total Opioid Dose (MME; mean ± SEM)	4.4 ± 0.5 mg	0.9 ± 0.4 mg	P < 0.001
Patients Receiving Supplemental IV Medications			
Adrenergic Agonist Use	40.0%	19%	P = 0.015
IV Acetaminophen	90%	38%	P < 0.001
Naloxone	0%	0%	N/a
Phase I PACU Time			
Phase I PACU time (minutes; mean)	54.9	36.3	P < 0.001

Tvetenstrand CD, et al. J Clin Anesth Pain Manag. 2020;4(2):123-8.

Research Article

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A Medication Use Evaluation of Sufentanil Sublingual Tablet 30 mcg for the Perioperative Management of Surgical Pain

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Citation: Koth MC, Shannon MH, James CS, Mark DC (2020) A Medication Use Evaluation of Sufentanil Sublingual Tablet 30 mcg for the Perioperative Management of Surgical Pain. Vol.8 No.5:6

Abstract

Background: Our institution conducted a medication use evaluation of a novel sublingual opioid for use as an analgesic in the perioperative setting for a wide variety of surgical procedures to compare perioperative opioid utilization and recovery times between two different opioid dosing protocols.

Method and Materials: Patients undergoing a surgical procedure requiring opioid-level analgesia were dosed sublingually with a sufentanil sublingual tablet 30 mcg in place of a standard dose of intravenous opioid (fentanyl, hydromorphone, or morphine) typically used for the procedure. The total dose of intraoperative and postoperative morphine milligram equivalents was calculated as well as the time in the recovery unit.

Results: Overall, 140 patients were dosed perioperatively with the sublingual sufentanil tablet from June 2019 to March 2020 and compared to 158 matched control patients undergoing similar surgeries with the same surgeons over a similar time period. Dosing of the tablet was either just prior to induction or intraoperatively in 137/140 of the patients, whereas 3 patients received a dose only in the recovery unit. The majority (90%) of patients required only a single tablet, while 14 patients required one additional dose in the recovery unit. The sufentanil sublingual tablet reduced opioid dosing requirements in the recovery unit by greater than 50% ($p<0.001$) compared to traditional intraoperative intravenous opioid dosing and resulted in an overall decrease in recovery discharge time by 14 min ($p<0.001$).

Conclusion: Perioperative sufentanil sublingual tablet administration can provide enhanced recovery compared to standard intravenous opioid administration.

Keywords: Postoperative; Acute pain; Opioid analgesic

Results

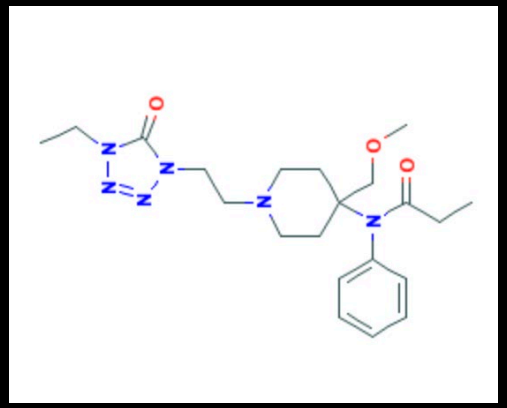
	Control (n = 158)	SST (n = 140)	P-value:
Intraoperative Opioid Use			
Intraoperative Total Opioid Dose (MME; Mean ± SEM)	15.7 ± 0.7 mg	9.6 ± 0.5 mg	P < 0.001
Postoperative Opioid Use (Overall)			
Patients Requiring Any Opioid in the Phase 1 PACU Period	83.5%	51.4%	P < 0.001
Postoperative Total Opioid Dose (MME; mean ± SEM)	3.6 ± 0.4 mg	8.1 ± 0.5 mg	P < 0.001
Patients Receiving Supplemental Medications			
Antiemetic Use (Percent Incidence)	16.5%	10%	N/a
Naloxone (Percent Incidence)	1.9%	0%	N/a
Phase 1 PACU Recovery Time			
Phase 1 PACU time (minutes; mean)	80	66	P < 0.001

Cassavaugh KM, et al. Journal of Universal Surgery. 2020; 8(5:6): 1-5 DOI: 10.36648/2254-6758.8.5.136

Alfentanil and Remifentanil

Alfentanil

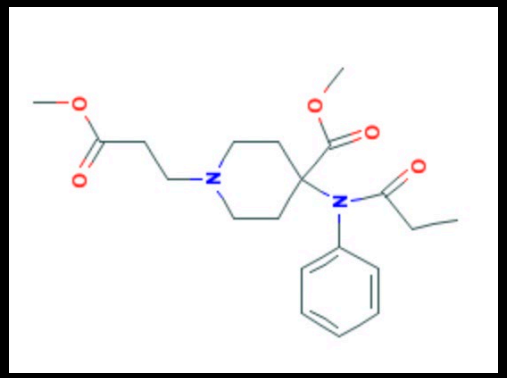
- First synthesized in 1976
- FDA approved for IV use as an anesthetic in 1987



https://pubchem.ncbi.nlm.nih.gov/compound/Alfentanil

Remifentanil

- First synthesized in early 1990s
- FDA approved for IV use in 1996



https://pubchem.ncbi.nlm.nih.gov/compound/Remifentanil#section=2D-Structure

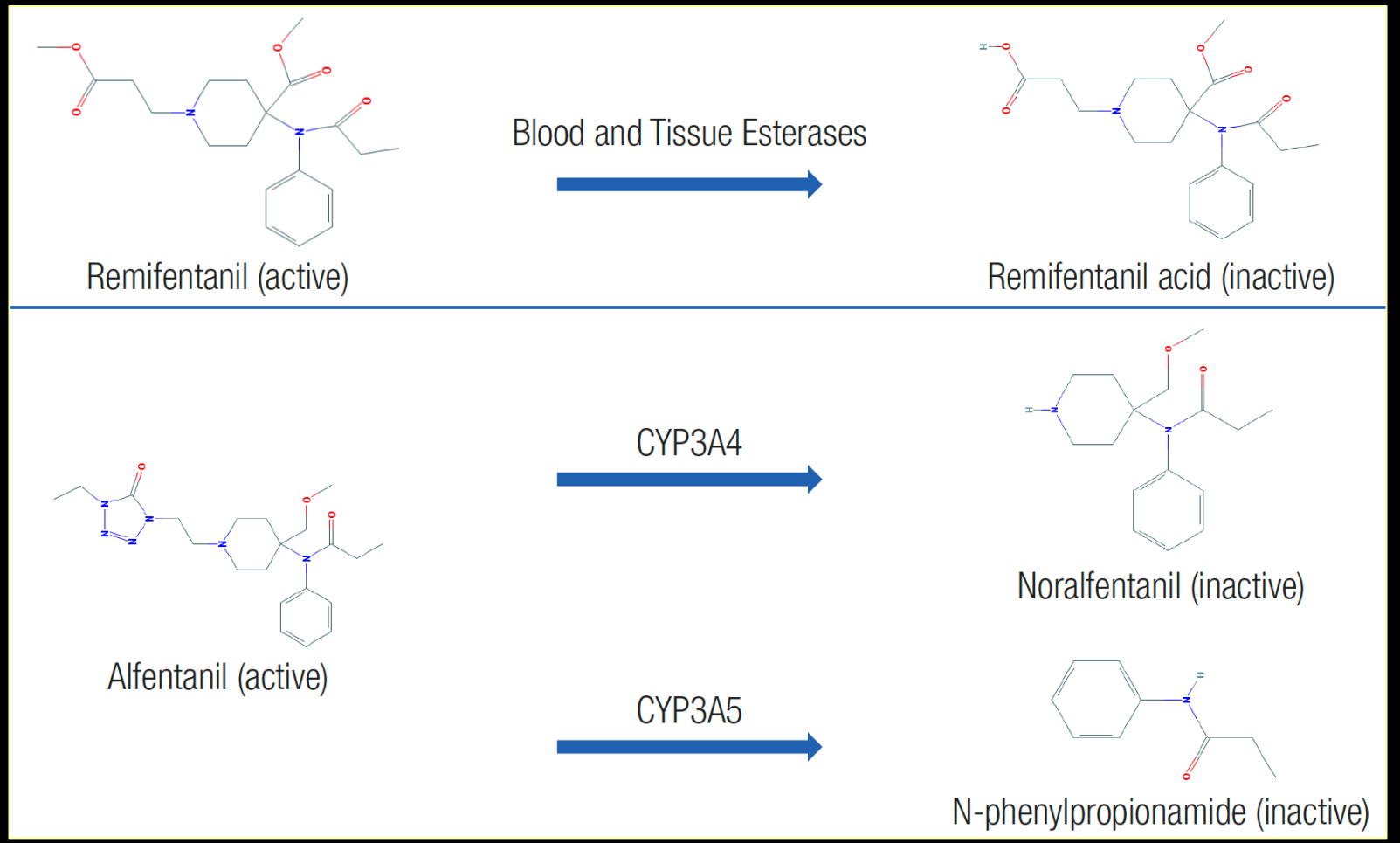
1. Niemegeers CJE, Janssen PAJ. Alfentanil (R 39 209) - a particularly short-acting intravenous narcotic analgesic in rats. *Drug Dev. Res.* 1981;1(1):83–88.
2. Buerkle HDS, Van Aken H. Remifentanil: a novel, short-acting, μ-opioid. *Anesth. Analg.* 1996;83(3):646–651

Pharmacokinetic Differences:

	Route of Administration	Bioavailability	Protein Binding	Terminal Half-Life	Antinociceptive Potency Ratio to Morphine
Remifentanil	IV only	100%	70%	3-10 minutes	100-200
Alfentanil	IV only	100%	92%	90-110 minutes	25

Bettinger JJ, Fudin J, Schatman M, et al. Fentanyl: Separating fact from fiction. Practical Pain Management. 2018;18(6):59-67

Metabolism



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Bettinger JJ, Fudin J, Schatman M, et al. Fentanyl: Separating fact from fiction. Practical Pain Management. 2018;18(6):59-67

Carfentanil

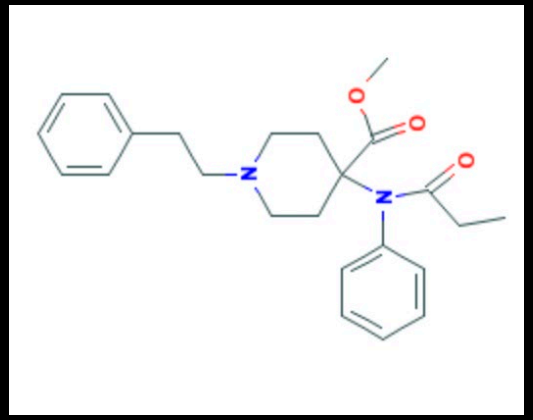
- First synthesized by Janssen Pharmaceuticals in 1974
- Introduced in Veterinary Medicine in 1986
  - Approved for use as a tranquilizing agent for elephants and other large mammals
- Currently Schedule II status by DEA and FDA
  - NOT APPROVED FOR HUMAN USE
- One of the “pharmaceutical” fentanyls that have been increasingly found in outbreaks
  - Though some data suggests potential reductions in illicit supply
- Exists as a white granular powder or clear water-soluble liquid (citrate)

Delcher C, Wang Y, Vega RS, et al. Carfentanil Outbreak – Florida, 2016-2017. MMWR. 2020;69(5);125-12

Carfentanil Vs. Fentanyl

Carfentanil

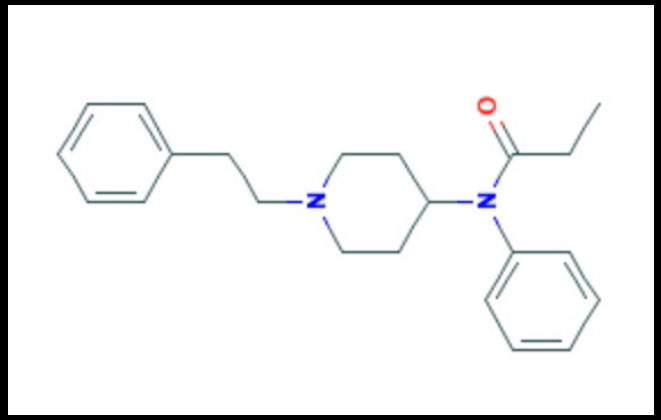
- Terminal half-life: ~5.7 hr
- Antinoceceptive potency ratio to morphine: ~10,000



https://pubchem.ncbi.nlm.nih.gov/compound/Carfentanil

Fentanyl

- Terminal half-life (IV): 2-4 hr
- Antinoceceptive potency ratio to morphine: 80 to 100



https://pubchem.ncbi.nlm.nih.gov/compound/Fentanyl

Bettinger JJ, Fudin J, Schatman M, et al. Fentanyl: Separating fact from fiction. Practical Pain Management. 2018;18(6):59-67

What About Those Illicitly Manufactured?

Major Problems

- Illegally created and chemically altered, often in clandestine labs
  - No regulation
- Can be difficult to not only identify for patients suffering from substance use disorders, but also by DEA, regulatory agencies
  - This can create dangerous situations, but also make it impossible sometimes for community resources to successfully identify ‘outbreaks’
- Potency data (if even available) often based on animal studies
- Scarce controlled human data on pharmacokinetic and pharmacodynamic characteristics

Acryloyl (Acryl) Fentanyl

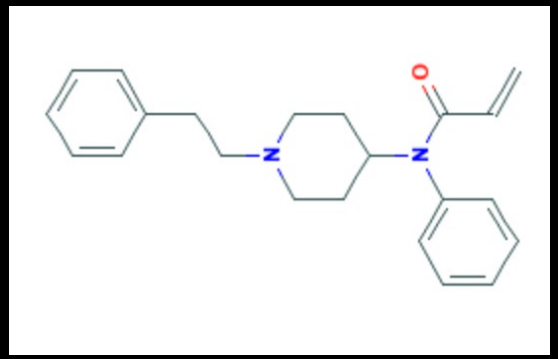
- First identified in Europe and US in 2016
  - First studied as a fentanyl analogue in the 1980s
- Zhu et al studied ED50 values compared to pharmaceutical fentanyl and morphine in hot-plate testing in mice
  - Found to be ~169-224 times more potent than morphine
- Maryanoff et al also studied mu-opioid receptor binding affinity in rat brain
  - IC50 values of 4.2, 1.6, and 1.4 for morphine, fentanyl, and acryloyl fentanyl respectively, indicating much greater binding affinity

Maryanoff BE, Simon EJ, Gioannini T, Gorissen H. Potential affinity labels for the opiate receptor based on fentanyl and related compounds. *J Med Chem.* 1982;25(8):913-919.

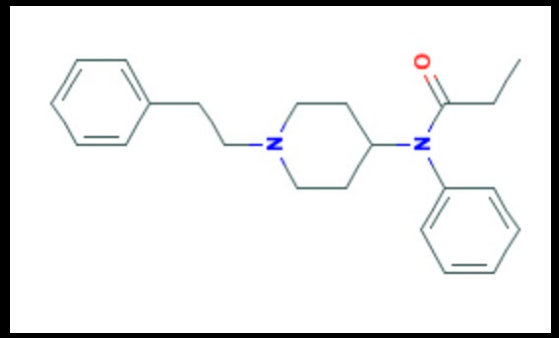
Comparison to Fentanyl

Chemical Name	Antinociceptive Potency Ratio to Morphine	Antinociceptive Potency Ratio to Fentanyl	Partition Coefficient[a]
Fentanyl	80-100	-	4.05
Acryl fentanyl OR acryloyl fentanyl[1,2]	169.5[b]	0.76[b]	4.2

[a]Log P corresponds to the logarithm of the ratio of the concentrations of the studied compound in octanol and in water: LogP = Log (C_{oct}/C_{water}).
[b]Antinociceptive potency ratio was calculated by comparing median effective dose (ED50) values in mice after hot plate and/or writhing episode testing



Acryloyl Fentanyl



Fentanyl

1. Ujvary I, Jorge R, Le Ruez T, et al. Acryloylfentanyl, a recently emerged new psychoactive substance: a comprehensive review. Forensic Tox. 2017;35(2):232-243
2. Maryanoff BE, Simon EJ, Gioannini T, et al. Potential affinity labels for the opiate receptor based on fentanyl and related compounds. J Med Chem. 1982;25(8):913-9
Images: https://pubchem.ncbi.nlm.nih.gov/compound/Acrylfentanyl; https://pubchem.ncbi.nlm.nih.gov/compound/Fentanyl#section=2D-Structure

Methyl Fentanyls

- Wide range of fentanyl analogues that have appeared on the black market since the 1980s
  - Most well known may be alpha-methyl fentanyl, AKA ‘China White’

- Several also synthesized for purposes of therapeutic drug development throughout the 80s
  - Alpha-methyl fentanyl[1]
  - 3-methyl fentanyl[1]
  - Beta-hydroxy-3-methyl fentanyl (ohmefentanyl)[2]

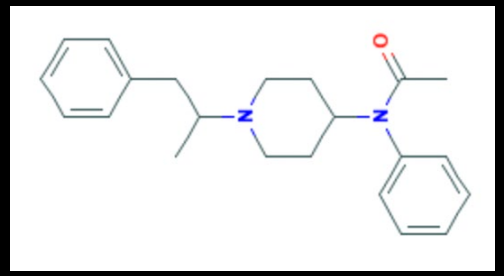
1. Higashikawa Y, Suzuki S. Studies on 1-(2-phenethyl)-4-(N-propionylanilino)piperidine (fentanyl) and its related compounds. VI. Structure-analgesic activity relationship for fentanyl, methyl-substituted fentanyls and other analogues. *Forensic Toxicology*. 2008;26(1):1-5.
2. Jin WQ, Xu H, Zhu YC, et al. Studies on synthesis and relationship between analgesic activity and receptor affinity for 3-methyl fentanyl derivatives. *Sci Sin.* 1981;24(5):710-720.

Comparison to Fentanyl

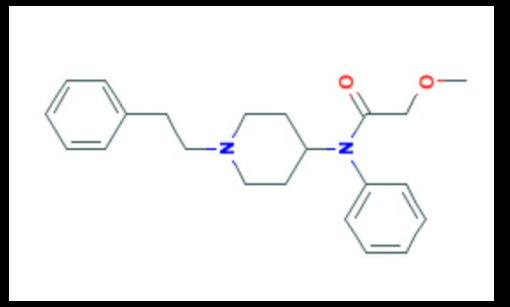
Chemical Name	Antinociceptive Potency Ratio to Morphine	Antinociceptive Potency Ratio to Fentanyl	Partition Coefficient[a]
Fentanyl	80-100[b]	-	4.05
Acetyl alpha-methyl fentanyl	3.1	0.06	~4
Alpha-methyl fentanyl	56.9[b]	1.1[b]	~4.5
Alpha-methylthio fentanyl	N/a	N/a	~4.4
Beta-hydroxy-3-methyl fentanyl (ohmefentanyl)	2957-6300[b]	13-28[b]	~3.6
Methoxyacetyl fentanyl	N/a	N/a	~3.5
3-methyl fentanyl	48.5-569[b]	0.9-10.5[b]	~4.5
3-methylthio fentanyl	N/a	N/a	N/a

[a]Log P corresponds to the logarithm of the ratio of the concentrations of the studied compound in octanol and in water: LogP = Log (C_{oct}/C_{water}).
[b]Antinociceptive potency ratio was calculated by comparing median effective dose (ED50) values in mice after hot plate and/or writhing episode testing

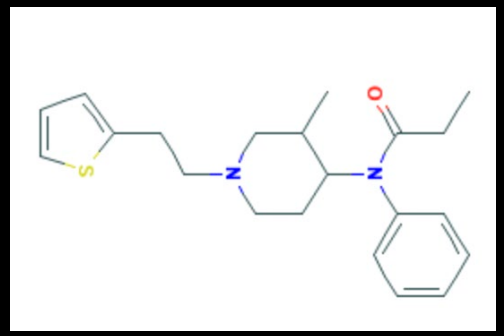
Bettinger JJ, Fudin J, Schatman M, et al. Fentanyl: Separating fact from fiction. Practical Pain Management. 2018;18(6):59-67



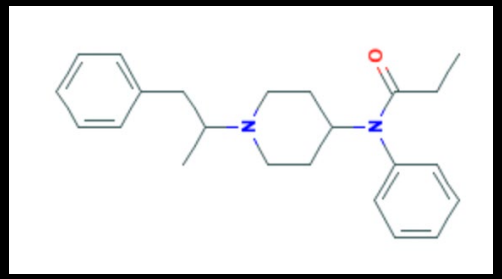
Acetyl-alpha-methylfentanyl



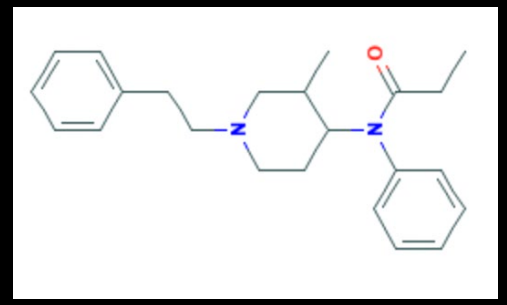
Methoxyacetyl fentanyl



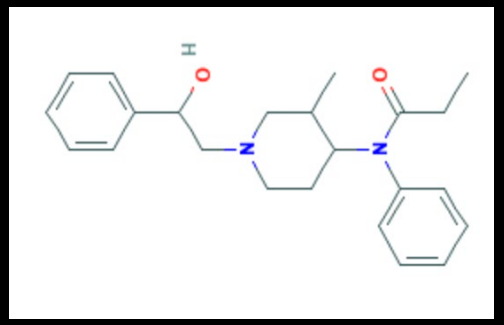
3-methylthiofentanyl



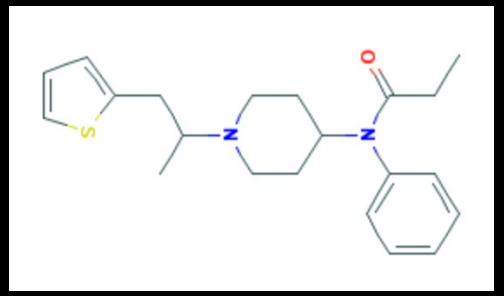
Alpha-methylfentanyl



3-methyl fentanyl



Ohmefentanyl



Alpha-methylthiofentanyl

Ocfentanil

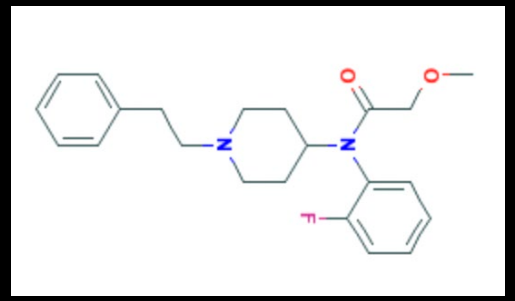
- Clinically investigated in the 1990s as a general anesthetic
  - Never gained FDA approval
- Abuse has varied since that time, though recently there have been increased reports across Europe of intoxication and death
- Ocfentanil was one of the only analogues studied in humans
  - ~200 times greater antinociceptive potency compared to morphine
  - PK data still scarce

Misailidi N, Papoutsis I, Nikolaou P, et al. Fentanyls continue to replace heroin in the drug arena: the cases of ocfentanil and carfentanil. Forensic Tox. 2018;36(1):12-32

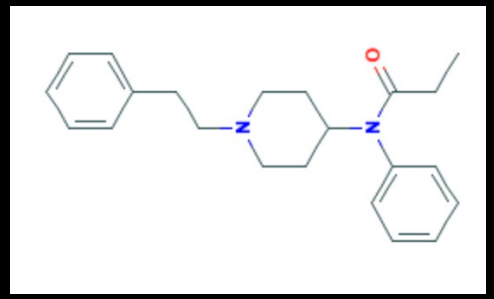
Comparison to Fentanyl

Chemical Name	Antinociceptive Potency Ratio to Morphine	Antinociceptive Potency Ratio to Fentanyl	Partition Coefficient[a]
Fentanyl	80-100	-	4.05
Ocfentanil	200[b]	~2.5[b]	4.2

[a]Log P corresponds to the logarithm of the ratio of the concentrations of the studied compound in octanol and in water: LogP = Log (C_{oct}/C_{water}).
[b]Antinociceptive potency ratio was calculated by comparing median effective dose (ED50) values in mice after hot plate and/or writhing episode testing



Ocfenatnil



Fentanyl

1. Misailidi N, Papoutsis I, Nikolaou P, et al. Fentanyls continue to replace heroin in the drug arena: the cases of ocfentanil and carfentanil. Forensic Tox. 2018;36(1):12-32
2. Glass P, Camporesi EM, Martel D, et al [Abstract only]. The analgesic efficacy of A3217. Anesthesiology. 1989;71(3A):A321
Images: https://pubchem.ncbi.nlm.nih.gov/compound/Ocfentanil; https://pubchem.ncbi.nlm.nih.gov/compound/Fentanyl#section=2D-Structure

Some Myths About Handling Fentanyl Analogues…

My skin was exposed to a fentalogue, I'm going to overdose!

My Skin Was Exposed… Will I Overdose?

- To date, NO TOXICOLOGICAL EVIDENCE supports opioid toxicity from accidental skin exposure or aerosolized fentalogues
- December 2017, both the American College of Medical Toxicology (ACMT) and American Academy of Clinical Toxicology (AACT) concluded:
  - "RISK OF CLINICALLY SIGNIFICANT EXPOSURE TO FENTANYL AND ITS ANALOGS TO EMERGENCY RESPONDERS IS EXTREMELY LOW…"
  - "TRANSDERMAL ABSORPTION OF FENTANYL POWDER IS EXTREMELY UNLIKELY TO OCCUR…"
- Finally, inert fentanyl powder is not aerosolized

Moss MJ, Warrick BJ, Nelson LS, et al. ACMT and AACT position statement: Preventing occupational fentanyl and fentanyl analog exposure to emergency responders. *J Med Toxicology*. 2017;13(4):347—351

How to Protect Oneself?

Patient Found Unresponsive, Potential Involvement Of Fentalogues… Do We Need A Higher Naloxone Dose?

Need Higher Doses of Naloxone?

- Higher binding affinities and greater potencies from different fentalogues can necessitate greater and more frequent doses of naloxone
- Moss et al in 2020 developed a model to predict naloxone concentrations high enough to displace fentanyl
  - At 75 ng/mL of fentanyl, 2mg IM naloxone failed to reduce fentanyl occupancy by 50%
- All of this meaning… Yes

Somerville NJ, O'Donnell J, Gladden RM, et al. Characteristics of fentanyl overdose - Massachusetts, 2014–2016. MMWR Morb Mortal Wkly Rep. 2017;66:382-386.
Moss RB, Pryor MM, Baillie R, et al. Higher naloxone dosing in a quantitative systems pharmacology model that predicts naloxonefentanyl competition at the opioid mu receptor level. PLoS One. 2020;15:e0234683.

New Naloxone Dose Approval?

- April 30, 2021, a new 8mg nasal spray naloxone was approved
- The newest dose at 8mg allows a higher serum naloxone compared to 0.4mg of IM naloxone and 2mg of IV naloxone
  - Slower onset
  - Still may require repeat dosing
- An important step in the “right” direction
  - However, several other barriers… Payer coverage, expense, stigmas, stereotypes, etc

Kloxxado Package Insert [Internet]. FDA. 2021. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212045s000lbl.pdf

Summary and Conclusions

- It is important to recognize that the “opioid crisis” is really a polysubstance and illicitly manufactured fentalogue crisis that our country is still trying to improve.

- Understanding the differences between pharmaceutical and illicitly manufactured fentalogues can play an important role in not only correctly identifying root causes to the crisis at play, but also in allowing for continued safe and effective use of pharmaceutical fentalogues in patients with pain conditions.

- Understanding myths versus facts in terms of fentalogue hysteria is essential in ensuring patients and emergency personnel remain safe.

Questions?

Thank You!

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