

Pharmacology of Fentanyl and Its Analogs: Implications for Treatment

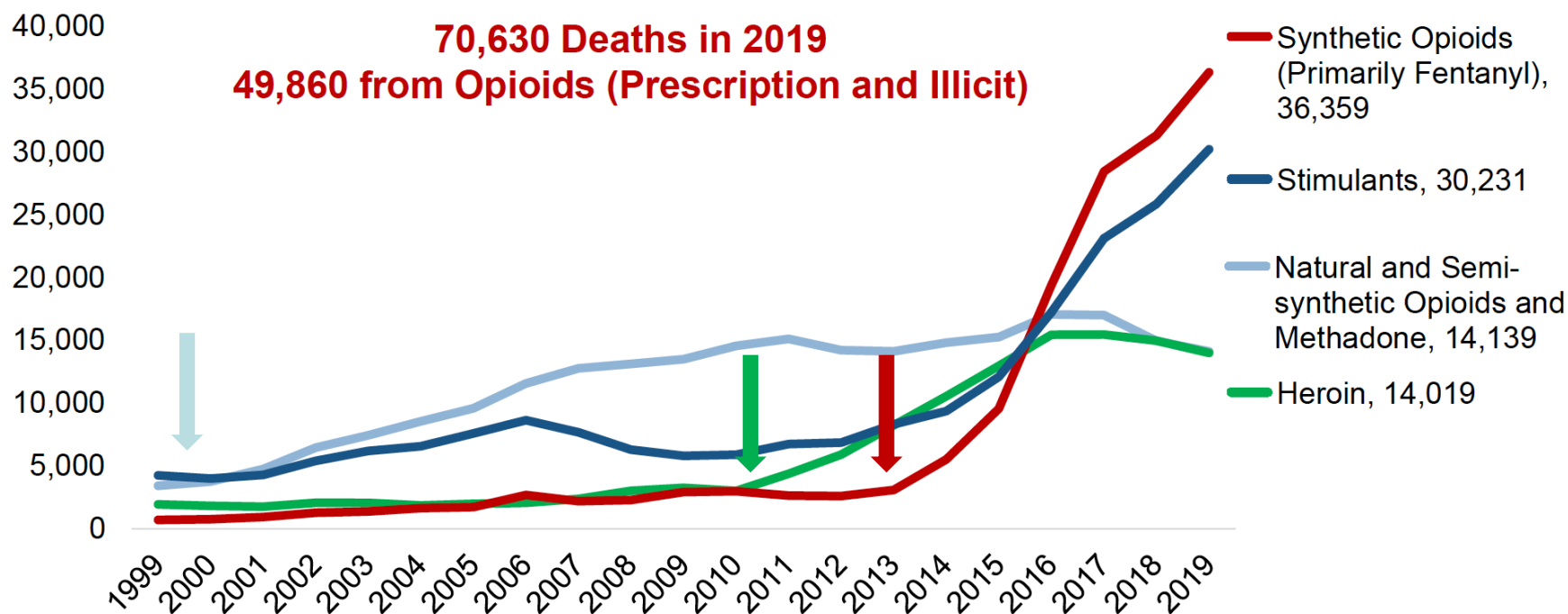
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Evolution of Drivers of Overdose Deaths, All Ages

Analgesics → Heroin → Fentanyl → Stimulants



Source: The Multiple Cause of Death data are produced by the Division of Vital Statistics, National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC), United States Department of Health and Human Services (US DHHS).

Increased Overdose Death Rates During COVID-19 Pandemic

12-months Ending July 2020 Compared to 12-months Ending July 2019

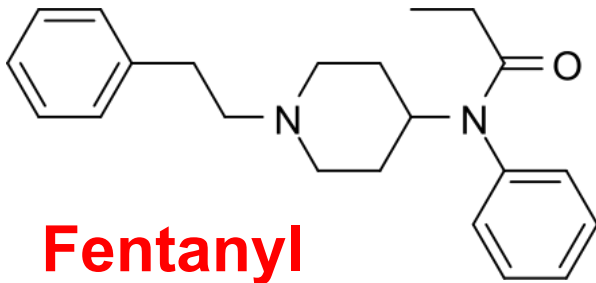
	ALL DRUGS	HEROIN	NAT & SEMI – SYNTHETIC	METHADONE	SYNTHETIC OPIOIDS	COCAINE	OTHER PSYCHO-STIMULANTS (mainly meth)
July 2019 *		14,793	12,203	2,875	33,704	15,031	14,941
March 2020*	75,687	14,145	12,349	2,837	40,756	17,465	18,033
July 2020*	86,001	14,427	13,259	3,315	50,122	19,542	20,406
July 2019-July 2020 Change	+24.2%	-2.5%	+8.7%	+15.3%	+48.7%	+30.0%	+36.6%



National Institute on Drug Abuse
Advancing Addiction Science

*NCHS Provisional Drug Overdose Death Counts: <https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm>

What is fentanyl?



- ✓ Potent synthetic opioid that is currently approved by the FDA
- ✓ First used medically in the 1960's as a general anesthetic
- ✓ Now used as a transdermal patch, lollipop, dissolving tablet and nasal spray for management of chronic or breakthrough pain

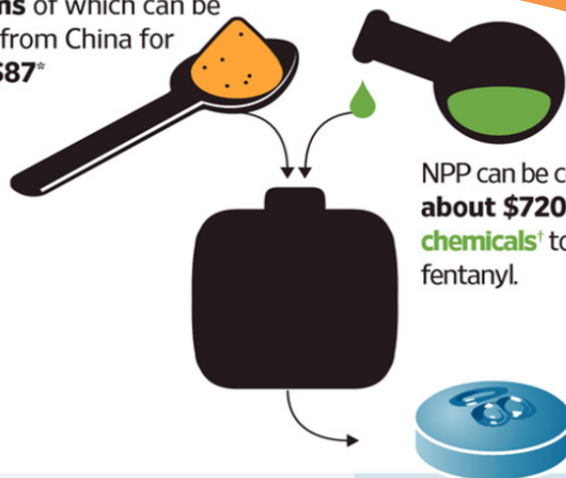
But **Pharmaceutical** Fentanyl is **Not** Driving the Current Epidemic

Fentanyl Synthesis from NPP

Criminal Chemistry

Traffickers manufacturing fentanyl often purchase the key ingredient from China

The key ingredient is **NPP**,
25 grams of which can be
bought from China for
about \$87*



NPP can be combined with
about \$720 of **other
chemicals**† to produce
fentanyl.

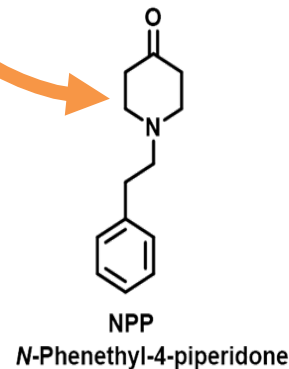
The resulting 25 grams of
fentanyl cost about \$810 to
produce...

...and are equivalent to up to
\$800,000 of pills on the black
market.

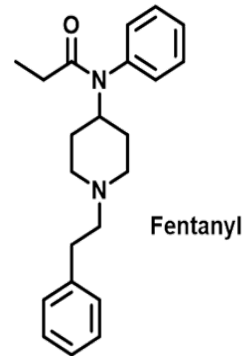
*Average current price from Chinese suppliers
Sources: NES Inc.; Drug Enforcement Administration;
Calgary Police

†Prices from U.S. suppliers

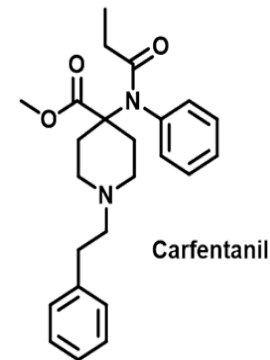
THE WALL STREET JOURNAL.



1. Reductive
Amination w/
Aniline
2. Acylation w/
Propanoyl Chloride

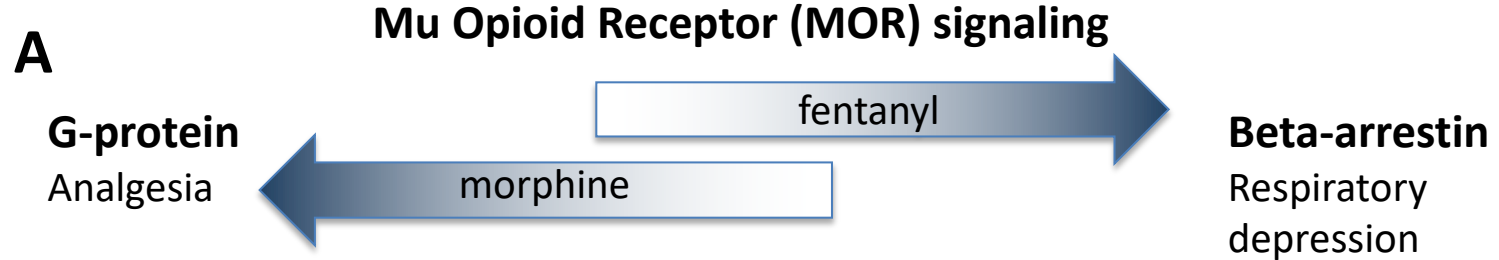


1. Potassium Cyanide,
Aniline, Acid
2. Methanol, Acid
3. Propanoyl Chloride



(Volkow, 2017)

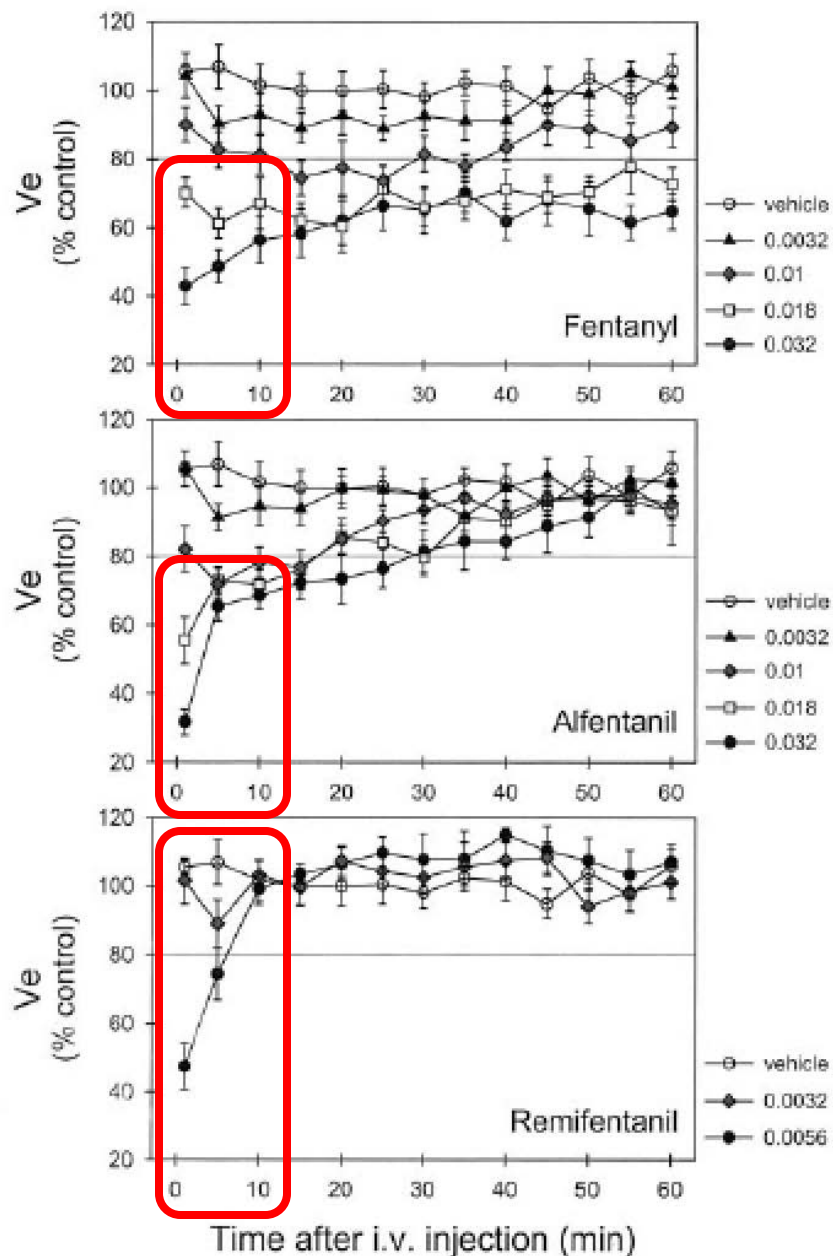
How does fentanyl differ from heroin (morphine)?

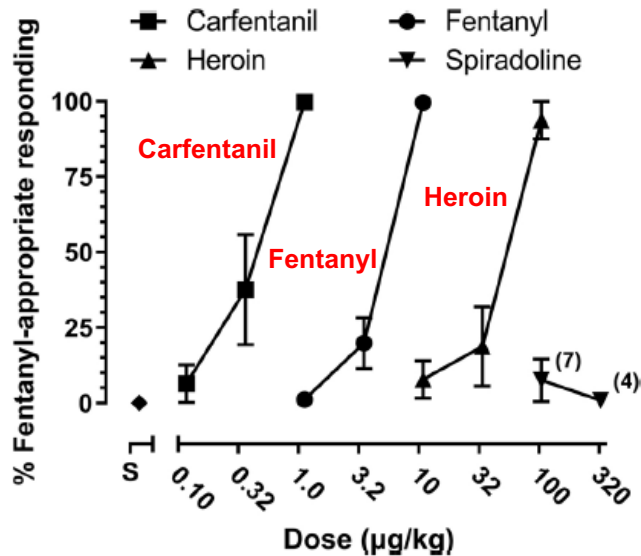


Morphine	Fentanyl
Little to no MOR internalization	MOR internalization
beta-arrestin 2 knockout (KO) mice No analgesic tolerance No locomotor sensitization Tolerance JNK-dependent	beta-arrestin-2 KO mice Tolerance not affected Locomotor sensitization not changed Tolerance JNK-independent
Tolerance is GRK3-independent	Tolerance is GRK3-dependent
RGS9-2 KO <i>increases</i> analgesia	RGS9-2 KO <i>decreases</i> analgesia
No ERK1/2 activation (via beta-arrestin-2)	ERK1/2 activation (via beta-arrestin-2)
Analgesic potency = 1	Equi-analgesic potency = 0.01* (i.e., fentanyl is ~100x more potent than morphine)
Less lipophilic	More lipophilic
Slow central nervous system (CNS) entry	Rapid CNS entry

Comer and
Cahill (2019)

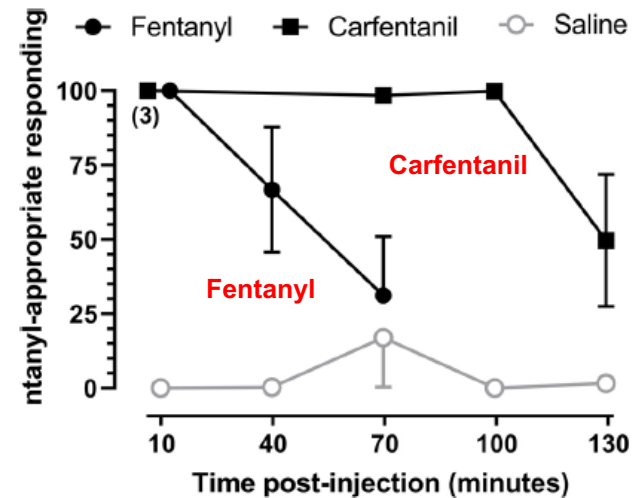
Fentanyl and its structural analogs can produce **profound decreases in respiratory depression in monkeys.**



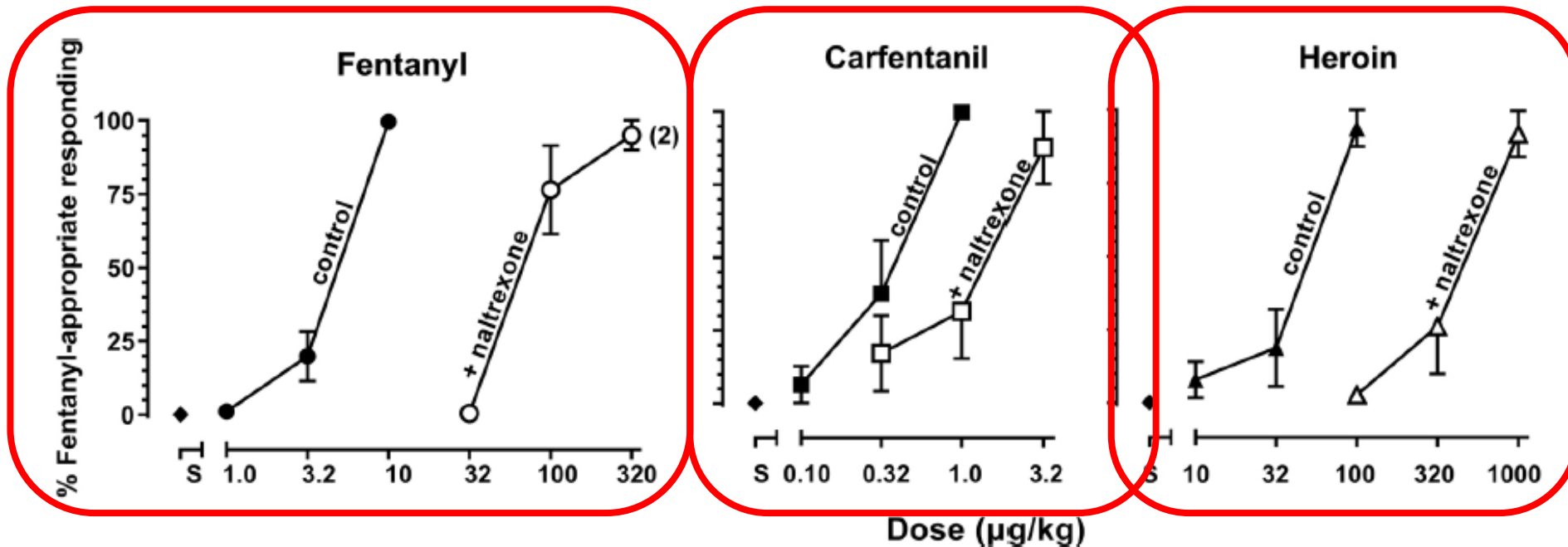


Fentanyl and carfentanil produce effects that are similar to heroin in rats

But carfentanil produces longer lasting effects than **fentanyl**



Although **naltrexone** antagonizes **fentanyl** and **heroin** to a similar extent, it is less effective against **carfentanil**.



But what about naloxone for
reversing fentanyl-related overdose?

Higher naloxone dosing may be required for opioid overdose

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Moss and Carlo *Substance Abuse Treatment, Prevention, and Policy*
<https://doi.org/10.1186/s13011-019-0195-4>

(2019) 14:6

Substance Abuse Treatment, Prevention, and Policy

DEBATE

Open Access

Higher doses of naloxone are needed in the synthetic opioid era



idity and Mortality Weekly Report

Ronald B. Moss* and Dennis J. Carlo

Characteristics of Fentanyl Overdose — Massachusetts, 2014–2016

Nicholas J. Somerville, MD^{1,2}; Julie O'Donnell, PhD^{1,3}; R. Matthew Gladden, PhD⁴; Jon E. Zibbell, PhD⁴; Traci C. Green, PhD⁵; Morgan Younkun, MD⁶; Sarah Ruiz, MSW²; Hermik Babakhanlou-Chase, MPH²; Miranda Chan, MPH²; Barry P. Callis, MSW²; Janet Kuramoto-Crawford, PhD¹; Henry M. Nields, MD, PhD⁷; Alexander Y. Walley, MD^{2,5}

Can J Anesth/J Can Anesth (2019) 66:414–421
<https://doi.org/10.1007/s12630-019-01294-y>

MMWR / April 14, 2017 / Vol. 66 / No. 14

US Department of Health and Human Services/Centers for Disease Control and Prevention

REVIEW ARTICLE/BRIEF REVIEW

Carfentanil: a narrative review of its pharmacology and public health concerns

Carfentanil: étude narrative de sa pharmacologie et problématiques de santé publique

Jessica L. S. Leen, MD · David N. Juurlink, MD, PhD

Special Section on The Opioid Crisis

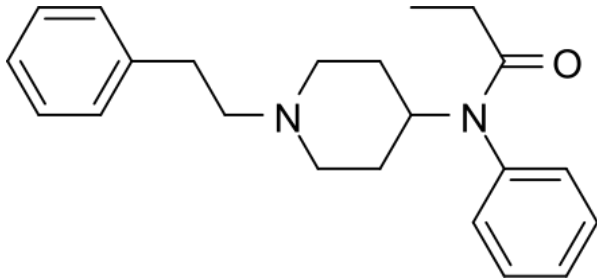
Noradrenergic Mechanisms in Fentanyl-Mediated Rapid Death Explain Failure of Naloxone in the Opioid Crisis

Randy Torralva and Aaron Janowsky

CODA Inc., Research Department, Portland, Oregon (R.T.); Research Service, VA Portland Health Care System, Portland, Oregon (R.T., A.J.); and Department of Psychiatry, Oregon Health & Science University, Portland, Oregon (R.T., A.J.)

Received April 2, 2019; accepted September 3, 2019

What can we conclude so far?



- ✓ Fentanyl is potent, has a rapid onset of action, and is short acting
- ✓ Naltrexone is effective in preventing the fentanyl-induced responses but is less effective against carfentanil
- ✓ Naloxone appears to be less effective against fentanyl overdose

MOUD for Fentanyl

- Limited data on methadone or buprenorphine or naltrexone on fentanyl associated OUD
- Methadone maintenance therapy (MMT) is effective in fentanyl OUD.
 - Retrospective study in RI showed that 6 months of MMT protected against death and promoted abstinence, but relapse rates were high ([Stone, et al., 2018](#)).
 - Repeated exposure to fentanyl common while in MMT, but no deaths for those who remained in treatment, 4 deaths in those who left treatment ([Stone, et al. 2020](#)).
- Buprenorphine is effective in fentanyl OUD ([Wakeman, et al., 2019](#)).
 - Harder to initiate patients on buprenorphine

Some hurdles...


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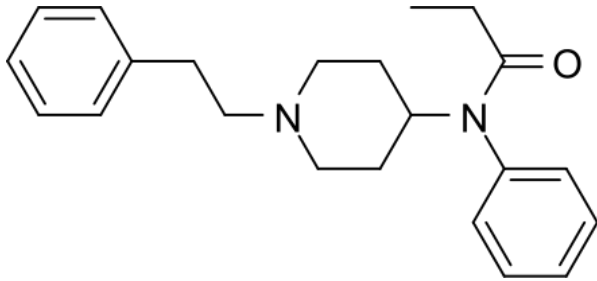
DOI: 10.1111/ajad.13069

Method for Successfully Inducting Individuals Who Use Illicit Fentanyl Onto Buprenorphine/Naloxone

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Unanswered Questions



- ✓ How well do methadone, buprenorphine, and naltrexone work for treating OUD in patients using fentanyl? What about the analogs?
- ✓ How do we most effectively transition patients from fentanyl to these treatment medications?
- ✓ How do we most effectively manage fentanyl-related overdoses?

Thank you!