Opioid Facts and Figures

Lauran Wirfs, DO
Addiction Medicine Fellow
University of Colorado SOM

Disclaimers

None

Objectives

- Learn about the pharmacokinetics of opioids
- Learn about the change in trends of illicit opioids
- Introduction to treatment modalities

History

- 3400 BC: first recorded history of poppy plant in Mesopotamia, known as "Joy Plant"
- 1700 BC: found in Babylonian medical tablets
- 1500 BC: records in Egypt, used for colic
- 460 BC: Hippocrates mentioned opium's "usefulness as a narcotic and styptic in treating internal diseases, diseases of women and epidemics."
- 129-219 AD: Galen, Greek physician, used opium in treatments
- 16th century: Paracelsus, Swiss alchemist, created Laudanum
- 17th century: British physician Thomas Sydenham created Laudanum tincture, mixed in wine/spirits
- 1804: Morphine isolated: "God's own medicine"
- 1874: Heroin discovered, manufactured in 1895
- 1905: US bans opium
- 1914: 1914 Harrison Narcotic Act

History

- 1937: Methadone synthesized in Germany due to opioid shortage
- 1959: Fentanyl synthesized by Dr. Paul Janssen, found to cross the BBB very effectively, stronger than morphine, wore off more rapidly
- 1970: Methadone approved by FDA for detox
- 1973: DEA created under Nixon
- 1974: Dr. Janssen synthesized carfentanil "found to sedate elephants, rhinoceroses, and other large animals"
- 1995: Oxycontin approval with Purdue Pharma
- 1996: American Pain Society creates fifth vital sign "pain"

Pharmacodynamics and Pharmacokinetics

Opioid Receptors

Mu (μ) opioid receptor: associated with euphoria and reward

Kappa (κ) opioid receptor: associated with anhedonia and dysphoria

Delta (δ) opioid receptor

Opioid effects: nausea, drowsiness, miosis, constipation (decreased motility), decreased respiratory drive, analgesia, xerostomia (dry mouth), nasal congestion, itching, sedation

37yo F with chronic back pain presents to the ED. States she was being prescribed oxycontin 10mg QID for her pain. Now her prescribing physician wants to cut back and is only giving her 10mg QD. She started to notice more yawning, sweating, nausea, abdominal cramping, loose stools and her back pain is even worse. She appears anxious in your room. She states she has never felt like this before. When she takes the oxycontin it helps for an hour or so but then she starts to feel the same way.

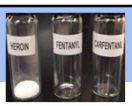
What has happened?

Even though this person based on the vignette doesn't have an opioid use disorder, she does have dependence. The rapid removal of opioids has caused her to go into withdrawal.

Withdrawal symptoms: anxiety, diaphoresis, piloerection, yawning, nausea/vomiting, diarrhea, abdominal cramping, mydriasis, tachycardia, restlessness, bone/joint aches, rhinorrhea, tremor

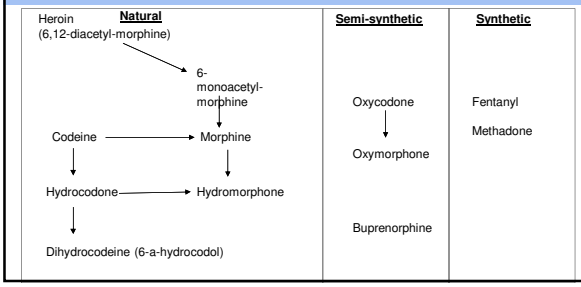
Opioid conversions

Drug	Approximate equivalent oral dose	Approximate equivalent IV or subcutaneous dose	Conversion ratio to determine daily total ORAL MME
Morphine	30mg	10mg	1:3 (parenteral:oral)
Fentanyl	NA	100 mcg**	1:300 (parenteral fentanyl:oral morphine)
Hydrocodone	30mg	NA	1:1
Hydromorphone	7.5mg	1.5mg	1:1 (oral hydromorphone:oral morphine)
Oxycodone	20mg	NA	1:1.5
Oxymorphone	10mg	1mg	1:3 (oral:oral) 1:30) parenteral to moporal

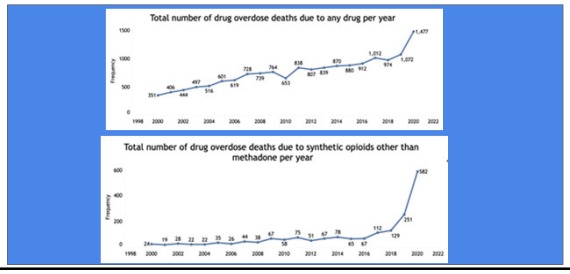


	Morphine	Heroin	Fentanyl
Half-life	3-5 hours	7-8 min (heroin) 20 min (6-acetylmorphine) (morphine)	4 hours IV
Bioavailability	40-50% PO	53% IH	70% IH
Ratio to morphine IV		2:1	100:1

Metabolism



New Trends


Total number of drug overdose deaths due to any drug per year
Frequency
1500
1000
500
0
351
406
444
497
516
501
619
728
739
764
653
838
807
870
839
880
912
1,012
974
1,072
1,477
1998
2000
2002
2004
2006
2008
2010
2012
2014
2016
2018
2020
2022
Total number of drug overdose deaths due to synthetic opioids other than methadone per year
Frequency
600
400
200
0
24
19
28
22
22
35
26
44
38
67
58
75
51
67
78
65
67
112
129
231
582
1998
2000
2002
2004
2006
2008
2010
2012
2014
2016
2018
2020
2022

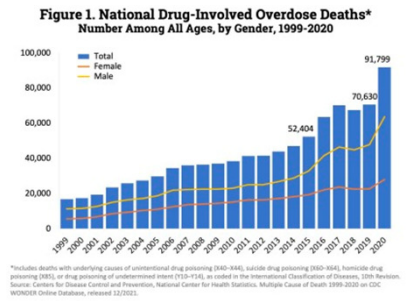


Figure 1. National Drug-Involved Overdose Deaths*
Number Among All Ages, by Gender, 1999-2020
100,000
80,000
60,000
40,000
20,000
0
Total
Female
Male
91,799
70,630
52,404
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
*Includes deaths with underlying causes of unintentional drug poisoning (X40–X44), suicide drug poisoning (X60–X64), homicide drug poisoning (X85), or drug poisoning of undetermined intent (Y10–Y14), as coded in the International Classification of Diseases, 10th Revision. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2020 on CDC WONDER Online Database, released 12/2021.

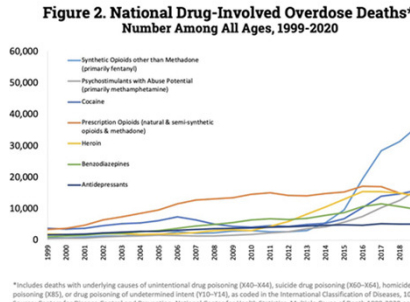


Figure 2. National Drug-Involved Overdose Deaths*,
Number Among All Ages, 1999-2020
60,000
50,000
40,000
30,000
20,000
10,000
0
Synthetic Opioids other than Methadone (primarily fentanyl)
Psychostimulants with Abuse Potential (primarily methamphetamine)
Cocaine
Prescription Opioids (natural & semi-synthetic opioids & methadone)
Heroin
Benzodiazepines
Antidepressants
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
*Includes deaths with underlying causes of unintentional drug poisoning (X40–X44), suicide drug poisoning (X60–X64), homicide drug poisoning (X85), or drug poisoning of undetermined intent (Y10–Y14), as coded in the International Classification of Diseases, 10th Revision. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2020 on CDC WONDER Online Database, released 12/2021.

Fentanyl

- Fentanyl half life close to 4 hours IV but as it is lipophilic, redistribution can occur, prolonging the withdrawal phase, delaying the start of induction
- Street fentanyl is equivalent to 500mcg to 2000mcg per tablet (DEA analysis has found counterfeit pills ranging from .02 to 5.1 milligrams)
- Around 42% of the fentanyl tested by the DEA is around 2000mcg
- Increase in adulterated cocaine and methamphetamine with fentanyl (0.9% to 17.6%; 0.9% to 7.9% respectively, from 2013 to 2018)
- National overdose deaths with synthetic opioids has risen over 55.6% over the last year
- In 2020, New York state had 184 overdose deaths due to methamphetamine with 82.6% involved with fentanyl. Methamphetamine overdose with fentanyl rose from 0.1 per 100,000 in 2016 to 1.4 in 2020, a jump by 1300%. Just methamphetamine went from 0.2 per 100,000 to 0.3

Fentanyl

- Dose: typically in tablets, however, now powder is being seen
- Route: Usually IH/IN/PO however, with powder being seen now, IV as well
- Frequency: can vary, from once a day to every hour

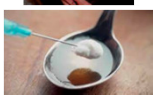
Opioid use

Orally: generally rx opioids

Intranasally: use of straws, flonase bottles, etc.

Inhalational: use of a pipe, tinfoil

IV: use of needles, cotton/"filters", water/dissolvent



Health Risks

- IVDU:
  - Increase risk of infectious diseases such as HIV/HCV/HBV
  - Increase risk of SSTI
  - Increase risk in sepsis/endocarditis/etc.
- Smoking
  - Increase risk of burning of oral mucosa/fingers, which can lead to increase risk of infections/spread of infectious diseases
- Stimulant use
  - Increase in high-risk sexual behaviors, leading to an increase risk in STIs, especially cocaine
  - Increase risk of dry mouth, leading to poor dentition and infections

Harm Reduction Education

Wash/sanitize hands/skin before injection

One needle= one injection

Avoid sharing needles

Avoid using alone

Use sterile water

Use sterile cotton if you have to use cotton

Consider a test dose

Harm Reduction Education

If also using stimulants, advise use of lubricants/condoms, stay hydrated and frequently drink water, chew gum, etc to prevent dental decay

If smoking, use a rubber stopper or some type of barrier on their pipe to prevent burns to their mouth, also recommend using their own pipe

Referrals

Local Syringe Exchange Program

Infectious disease for Hep C, HIV treatment

Substance use treatment

Mental health services

Treatment

Methadone

Full Agonist

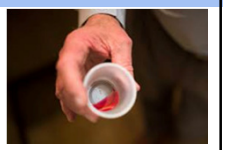
Formulations: tablet, liquid

Usual dose can range from 40-100mg, now increasing though

Can only be given through an OTP (Opioid Treatment Program) for use disorders

Benefits: full agonist, pain control, stability with facility requirements for some people, no "max" dose, easy for induction, long half life (15-60hr)

Pitfalls: can be hard for patients with mobility/transportation issues, can interfere with work, increase risk of sedation, stigma, QTc prolongation, drug interactions, decrease testosterone



Buprenorphine (suboxone)

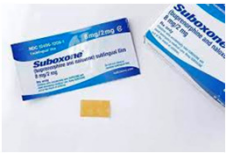
Partial agonist/antagonist

Usual dose: 8-24mg

Formulations: tablet, film, injectable

Benefits: No need for OTP, decrease risk of sedation, pain control, long acting (24-36hr), high affinity for mu receptor

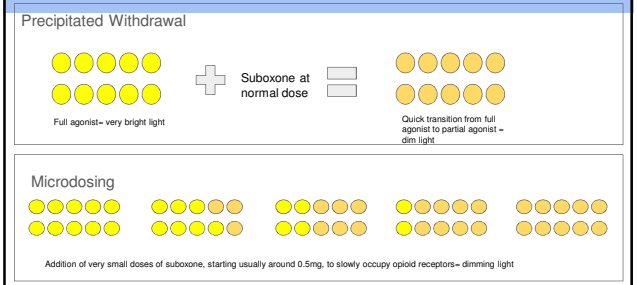
Pitfalls: max dose of 24mg, taste?, dental decay, operative management, induction, nausea/headaches



Suboxone induction in setting of fentanyl

- Guidelines currently recommend leaving a sufficient time period between the cessation of full agonist, such as fentanyl, and the initiation of buprenorphine
- Prolonged withdrawal/tapering of full agonists can lead to relapse in patient
- Micro-induction can initiate the induction of buprenorphine earlier with the hopes of not eliciting precipitated withdrawal and preventing relapse

Suboxone Induction in setting of fentanyl



Modified Bernese Method

Day	Dose
Day 1	0.5mg buprenorphine and continue full agonist
Day 2	0.5mg buprenorphine BID and continue full agonist
Day 3	1mg buprenorphine BID and continue full agonist
Day 4	2mg buprenorphine BID and continue full agonist
Day 5	4mg buprenorphine BID and continue full agonist
Day 6	8mg buprenorphine and continue full agonist
Day 7	8mg buprenorphine in AM, 4mg buprenorphine in PM and continue full agonist
Day 8	12mg buprenorphine and STOP full agonist

Naltrexone

Opioid antagonist

Forms: Tablet, IM injection

Benefits: opioid antagonist, no sedation

Pitfalls: induction, operative/pain management, nausea/headaches

Symptomatic Treatment

Medication	Schedule
Clonidine	0.1mg q4h x 2-3 days
Zofran	8mg BID
Loperamide	2mg QID
Gabapentin	600mg BID
Ibuprofen	600mg every 6hrs
Trazodone	50-100mg QHS
Tylenol	1000mg TID

References

- "Approximate Dose Conversions for Commonly Used Opioids (Refer to Important Note below)." *UpToDate*, https://www.uptodate.com/contents/image?imageKey=PALC%2F111216#!
- Dayer, Lindsey E., et al. "A Recent History of Opioid Use in the US: Three Decades of Change." *Substance Use & Misuse*, vol. 54, no. 2, 2018, pp. 331–339., https://doi.org/10.1080/10826084.2018.1517175.
- "Drug Overdose Deaths in the U.S. Top 100,000 Annually." *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention, 17 Nov. 2021, https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2021/20211117.htm.
- LaRue, Leah, et al. "Rate of Fentanyl Positivity among Urine Drug Test Results Positive for Cocaine or Methamphetamine." *JAMA Network Open*, vol. 2, no. 4, 2019, https://doi.org/10.1001/jamanetworkopen.2019.2851.
- "Opium throughout History | the Opium Kings | Frontline." *PBS*, Public Broadcasting Service, https://www.pbs.org/wgbh/pages/frontline/shows/heroin/etc/history.html.
- "Opium throughout History | the Opium Kings | Frontline." *PBS*, Public Broadcasting Service, https://www.pbs.org/wgbh/pages/frontline/shows/heroin/etc/history.html.
- "Overdose Death Rates." *National Institutes of Health*, U.S. Department of Health and Human Services, 1 June 2022, https://nida.nih.gov/drug-topics/trends-statistics/overdose-death-rates.
- Presley, Christopher C., and Craig W. Lindsley. "Dark Classics in Chemical Neuroscience: Opium, a Historical Perspective." *ACS Chemical Neuroscience*, vol. 9, no. 10, 2018, pp. 2503–2518., https://doi.org/10.1021/acschemneuro.8b00459.
- Rook, Elisabeth J, et al. "Population Pharmacokinetics of Heroin and Its Major Metabolites." *Clinical Pharmacokinetics*, vol. 45, no. 4, 2006, pp. 401–417., https://doi.org/10.2165/00003088-200645040-00005.
- Crude rates drug overdose deaths due to synthetic opioids mentioning fentanyl in Colorado, 2000-2020. Workbook: Drug overdose dashboard.
- "Department of Health." *Opioid-Related Data in New York State*, https://health.ny.gov/statistics/opioid/.
- Hämmig R, Kemter A, Strasser J, et al. Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method. Substance abuse and rehabilitation. 2016;7:99-105. doi:10.2147/SAR.S109919