Opioid Induced Hyperalgesia and Role of Medications for Opioid Use Disorder (MOUD)

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Objectives

- Overview of chronic pain neurobiology and pathophysiology of OIH
- Discuss treatment options in patients with OIH and chronic pain
- Brief review of OUD and path to MOUD
- Discuss role of MOUD in treatment of OIH and pain

Case

- 56 yo female, with past medical history of arthritis, chronic hepatitis C, HTN, mild asthma, and GERD, presents to the Addiction Psychiatry Clinic in May 2019.
- She reports a history of chronic pain which started after a course of interferon treatment for hepatitis C in 2008. Reporting diffuse arthralgia and myalgia. Reports “deep pain” in bones, muscles, and joints which is present “daily.”
- Pain is worsened by activity, and previously only relieved by opioid medications prescribed by her primary care provider, that include MS Contin 100 mg BID and Percocet 10-325 mg 4 times per day.
- Recently, higher dose of opioids have tended to paradoxically worsen her pain, which led her to use more medication. Patient has taken duloxetine and pregabalin in the past with minimal benefit. She reports allergy to NSAIDs.
- She presents to the addiction psychiatry clinic seeking help as her primary care provider wanted to transition her off the narcotic pain medications.

- At the Addiction Psychiatry clinic visit, patient reported excessive use of opioid pain medications to reduce her pain.
- She admitted to using more medication than prescribed due to excessive pain perception in an attempt to treat the pain unsuccessfully.
- She appeared frustrated that her pain became worse if she took very high doses and was confused why this would happen.
- She consistently she ran out of opioid medications early for months at a time. This caused her to have withdrawal symptoms and led her to seek early refills frequently, and at times getting them from family and friends.
- Patient appeared to be physiologically dependent on opioids and showed pharmacological tolerance and withdrawal. Patient met criteria for moderate opioid use disorder (OUD) along with possible underlying phenomenon not well understood.

VITALS: Blood pressure 151/76, pulse 76, temperature 98.3 °F (36.8 °C), height 1.715 m (5' 7"), weight **(!) 106.5 kg (234 lb)**

Lab Results

Component	Value	Date
HGB	12.6	05/08/2019
HCT	41.2	05/08/2019
PLT	423 (H)	05/08/2019

Lab Results

Component	Value	Date
NA	142	05/08/2019
K	4.0	05/08/2019
CL	98	05/08/2019
CO2	32 (H)	05/08/2019
GLU	105	05/08/2019

Lab Results

Component	Value	Date
INR	0.9	11/21/2010

- What is the underlying process going on which is causing increased perception of pain?
- What is the approach to patient with the above concern?
- What are the treatment recommendations or guidelines, if any?

Pain Pathway

- **Nociception**

  - The sensory mechanism that allows animals to sense and avoid potentially tissue-damaging stimuli, is critical for survival.

  - This process relies on nociceptors, which are specialized neurons that detect and respond to potentially damaging forms of energy — heat, mechanical and chemical — in the environment.

  - Nociceptors accomplish this task through the expression of molecules that function to detect and signal the presence of potential harm.

Pain Pathway

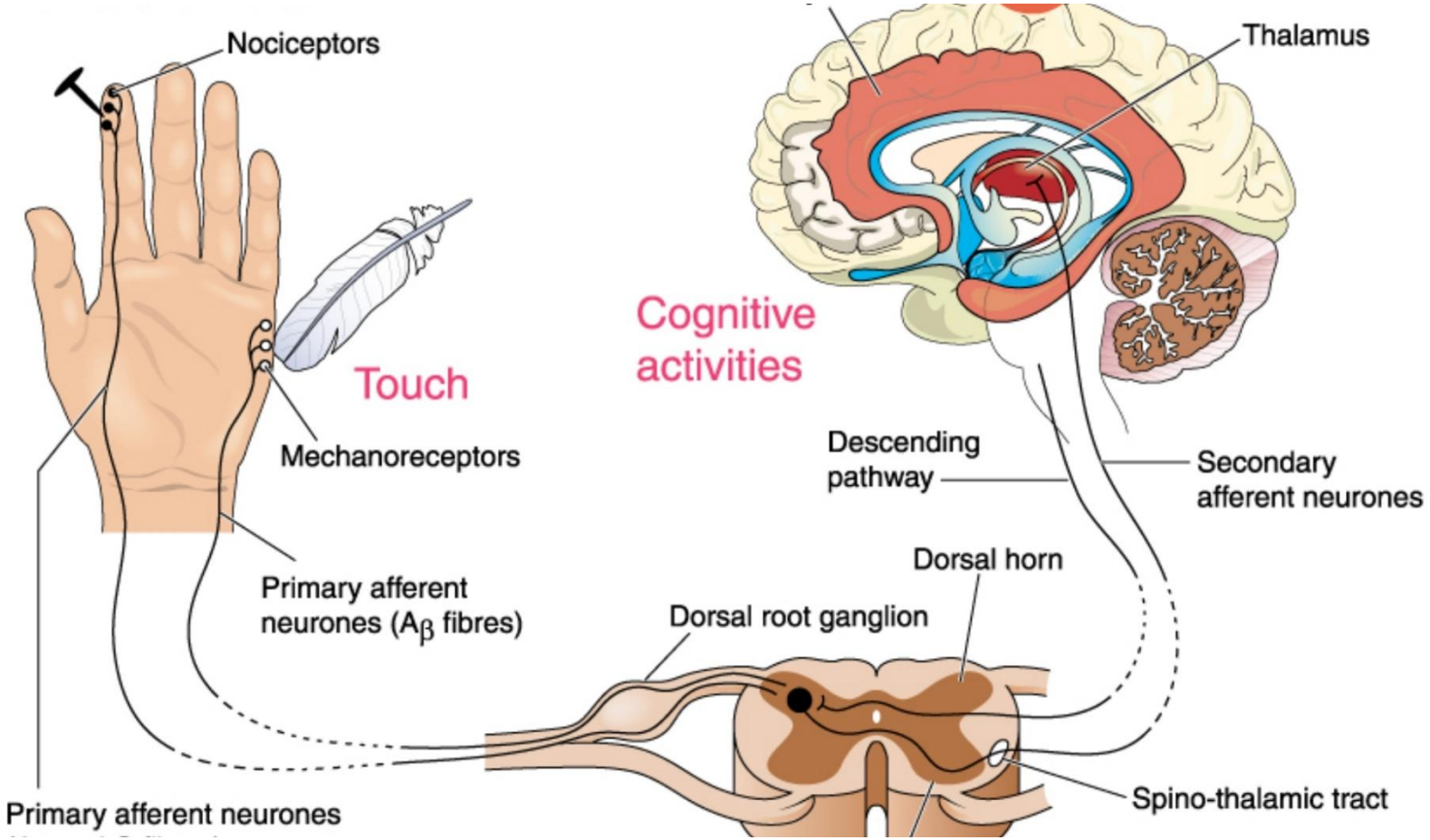
- **Anti-nociception**
  - Antinociception refers to the inhibition of the detection of a painful stimulus by nociceptive (pain) neurons.
  - Simple terms, blocking of the pain stimuli from reaching the brain.
- **Analgesia**
  - Alleviation of the experience of pain, which includes not only the inhibition of nociceptive signaling, but also a subjective component that cannot be assessed in animal models.

Pain Pathway

STIMULUS → COGNITIVE PERCEPTION

1. Pain reception and sensory afferent to spinal cord
2. Processing of pain in dorsal horn
3. Ascending pathways in the brain
4. Processing of painful stimuli in brain
5. Descending analgesic pathway

Pain Pathway



Opioid Induced Hyperalgesia

- Opioid-induced hyperalgesia (OIH) is defined as a state of nociceptive sensitization caused by acute or chronic exposure to opioids. The condition is characterized by a paradoxical response whereby a patient receiving opioids for the treatment of pain could become more sensitive to certain painful stimuli.
  - The type of pain experienced might be the same as the underlying pain or might be different from the original underlying pain.
  - OIH appears to be a distinct, definable, and characteristic phenomenon that could explain loss of opioid efficacy in some patients

Historical view

- Observed in patients given morphine for pain in early 19th century
- In 1870, observed by Albutt that potent analgesics could result in increase in pain
- Hyperalgesia also noted in methadone-maintained OUD patients
- Opioid metabolites shown to cause irritability and allodynia

- **Allodynia:** pain due to a stimulus that does not normally provoke pain. Can occur due to a number of conditions and injuries, including:

  - Migraines
  - Fibromyalgia
  - Complex regional pain syndrome (CRPS)
  - Diabetes
  - Postherpetic neuralgia (PHN)
  - Peripheral neuropathy
  - Multiple sclerosis (MS)

Clinical evidence

- Study showing development of OIH after intraoperative remifentanil infusion
- Patient with detox from opioids showing improvement in pain
- Higher pain sensitivity in patients on methadone for OUD
- Trial involving chronic low back pain and long acting morphine showed measurable hyperalgesia within 1-month of Rx start

OIH Mechanisms

5 mechanisms involving: (HYPOTHESIS!!)

1. The central glutamatergic system
2. Spinal dynorphins
3. Descending facilitation
4. Genetic mechanisms
5. Decreased reuptake and enhanced nociceptive response

Central Glutaminergic System

1. NMDA receptors when inhibited, prevent the development of pain tolerance leading to OIH

2. The glutamate transporter system is inhibited, therefore increasing the amount of glutamate available to NMDA receptors

3. Calcium regulated intracellular protein kinase C is likely a link between cellular mechanisms of tolerance and OIH

4. Cross talk of neural mechanisms of pain and tolerance may exist

5. Prolonged morphine administration induces neurotoxicity via NMDA receptor mediated apoptotic cell death in the dorsal horn.

Spinal Dynorphins (SD)

- Opioid peptides in the spinal cord that may play a role in chronic pain, opioid tolerance, and itch.
- Levels increase during chronic pain development and persist during chronic pain
- Knockout of the dynorphin gene prevents chronic pain in mice
- Works in the brain as a **κ-receptor agonist**

Spinal Dynorphins (SD)

- SD levels have shown increases with continuous infusions of μ-receptor agonists
- These increased levels lead to the release of spinal excitatory neuropeptides such as calcitonin gene related peptide (CGRP) from primary afferents
- OIH is therefore a pro-nociceptive process facilitated by increasing the synthesis of excitatory neuropeptides and their release upon peripheral nociceptive stimulation

COMT

- Catechol-O-methyltransferase (COMT) is an enzyme that breaks down catecholamines, drugs, and other substances.

- COMT helps maintain the levels of neurotransmitters like dopamine and norepinephrine in the brain.

Genetic Influences

- Genetic influence by the activity of COMT
- 3 possible genotypes of this polymorphism representing substitution of the amino acid valine for methionine
- The breakdown of dopamine and noradrenaline is up to 4 times higher resulting in different levels of synaptic dopamine/noradrenaline following neurotransmitter release
- This affects memory function, anxiety, and pain sensitivity regulation
- These mechanisms indicate that COMT influences central pain modulation

Clinical Prevalence

1. Former opioid users
2. Chronic pain patients
3. Patients given very high dose opioids

Challenges and limitations

- Animal research supports existence though robust human clinical studies lacking
- Studies limited to short-acting phenylpiperidine and piperidine opioids (remifentanil, alfentanil and fentanyl) with less focus on phenanthrene opioids (morphine and hydromorphone)
- Understanding of clinical differentiation of OIH and opioid tolerance remains challenging
- Prevalence of OIH is not known, and most reports attempting to quantify OIH prevalence are anecdotal and related to chronic high-dose opioid use

Differential diagnosis

Table 1. Comparison of opioid-induced hyperalgesia, tolerance, withdrawal and opioid use disorder.

	Opioid-induced hyperalgesia	Opioid tolerance	Opioid withdrawal	Opioid use disorder
Mechanism	Drug-induced pain sensitization within the CNS (central sensitization)	Decreased drug efficacy Desensitization of μ-receptor to opioids	Absence of μ-receptor stimulation Increased NE levels result in systemic symptoms	Uncontrolled use of opioids despite adverse outcomes Possible desensitization to opioids
Opioid escalation	Pain not overcome with opioid dose escalation	Pain overcome with opioid dose escalation	Symptomatic improvement with opioid escalation	Variable response to dose escalation
Other symptoms	Pain worse with dose escalation	Tolerance to many opioid side effects but not central apnea or constipation	Symptoms include muscle spasm, abdominal cramp, anxiety, palpitations, and hot flashes	Symptoms of tolerance and withdrawal, depending on the presence or lack of opioid use

CNS: Central nervous system; NE: Norepinephrine.

Screening strategies

Preoperative	Intraoperative	Postoperative

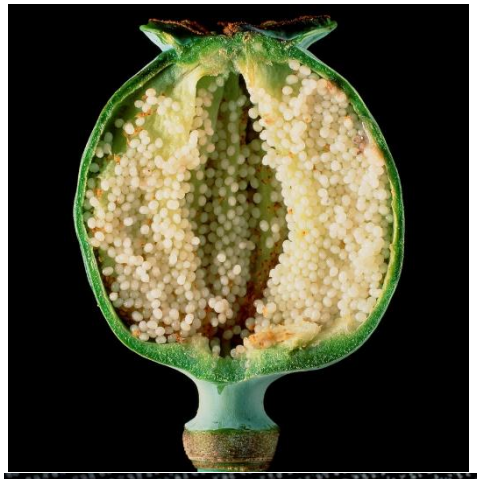
Weeks prior to surgery
• Identification of patient with increased OIH risk
• Nonpharmacologic strategies
  • Education
  • Social support
  • Psychological support
  • Relaxation techniques
• Taper preoperative opioids
 	
Day of surgery
• Consider regional analgesia
• Non-opioid analgesics
  • NSAIDs
  • Acetaminophen
	Opioid minimization
	• NMDA antagonist
	• α-2 agonist
	• β-blockers
	• NSAIDs
	• Regional analgesia
	
	Opioids
	• Supplemental analgesia (not first line)
	• Lowest possible infusion doses when needed
	• Consider methadone
		Opioid minimization
		• Nonpharmacologic strategies
		  • Early mobilization
		  • Caloric intake
		  • Education
		  • Social support
		  • Psychological support
		  • Relaxation techniques
		• Non-opioid analgesics
		  • NSAIDs
		  • Acetaminophen
		  • NMDA antagonists
		  • α-2 agonist
		• Regional analgesia
		• Opioids
		  • Supplemental analgesia (not first line)
		  • Consider methadone

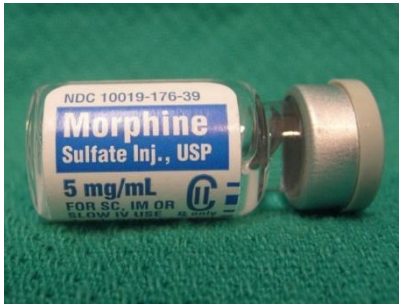
Treatment recommendations for OIH/Chronic pain

- Multimodal analgesia:
  - » Non-narcotic pain medications
  - » Nerve blocks
  - » Physical therapy
  - » Relaxation or biofeedback techniques
- Treatment goals:
  - » Less than 5/10 on the Likert scale
  - » Approximately 30-50% improvement over the long term
- Medications:
  - » NSAIDs
  - » Muscle relaxants
  - » TCAs
  - » SNRIs
  - » AEDs
  - » Buprenorphine

Commonly Known Opiates And Opioids

- **Opium extracts**
  - Morphine
  - Codeine
  - Thebaine
  - Tincture opium
- **Semi-synthetic**
  - Oxycodone
  - Hydrocodone
  - Hydromorphone
  - Oxymorphone
  - Diacetylmorphine
  - Buprenorphine
- **Synthetic**
  - Meperidine
  - Methadone
  - Tramadol
  - Fentanyl
  - U-47700
- **Newer synthetic opioids:**
  - Carfentanil
  - ~150 total known synthetics





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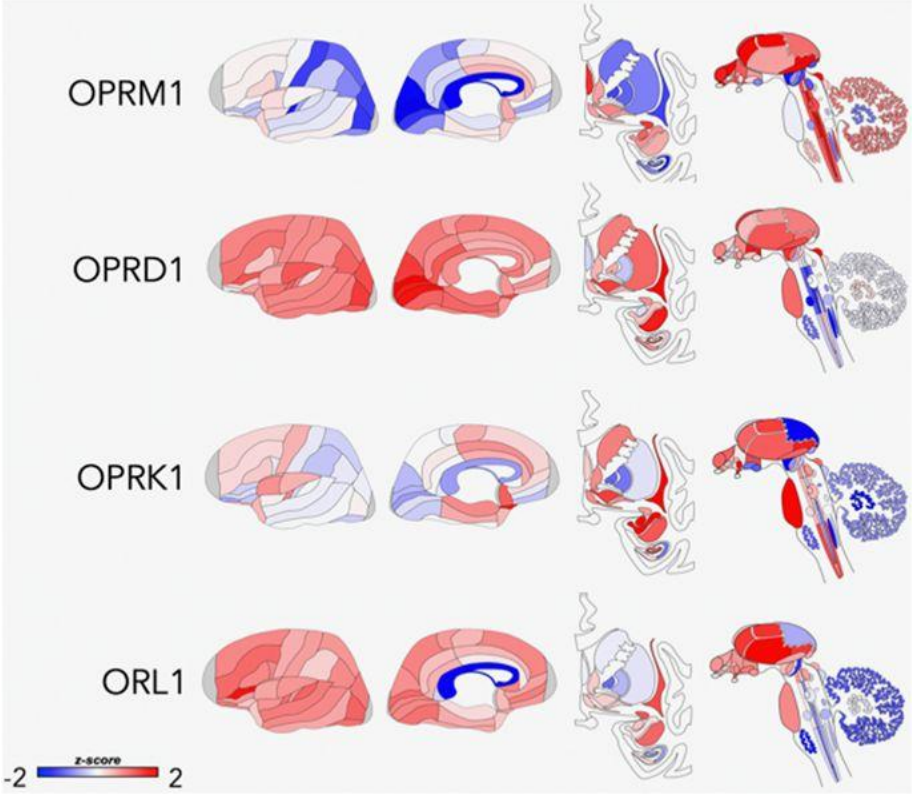
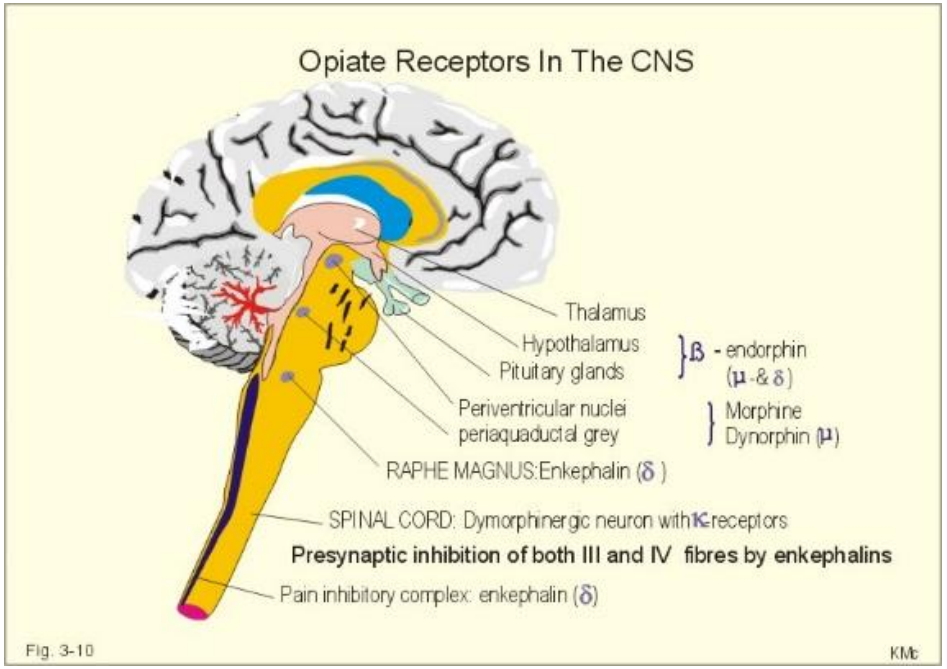
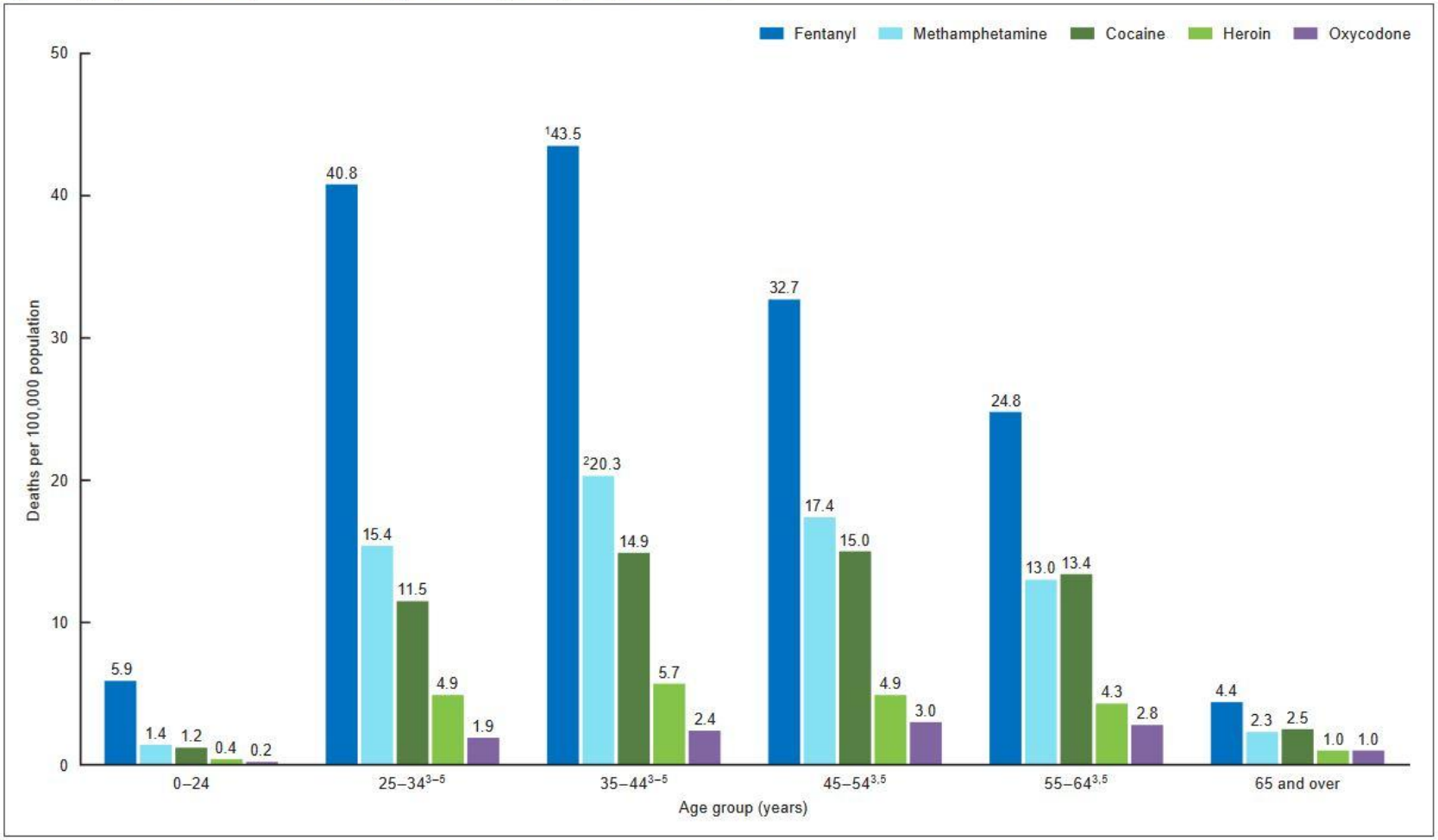
Opioid receptors in the brain





National Statistics

Figure 3. Age-specific rates of drug overdose deaths, by selected drugs and age group: United States, 2021



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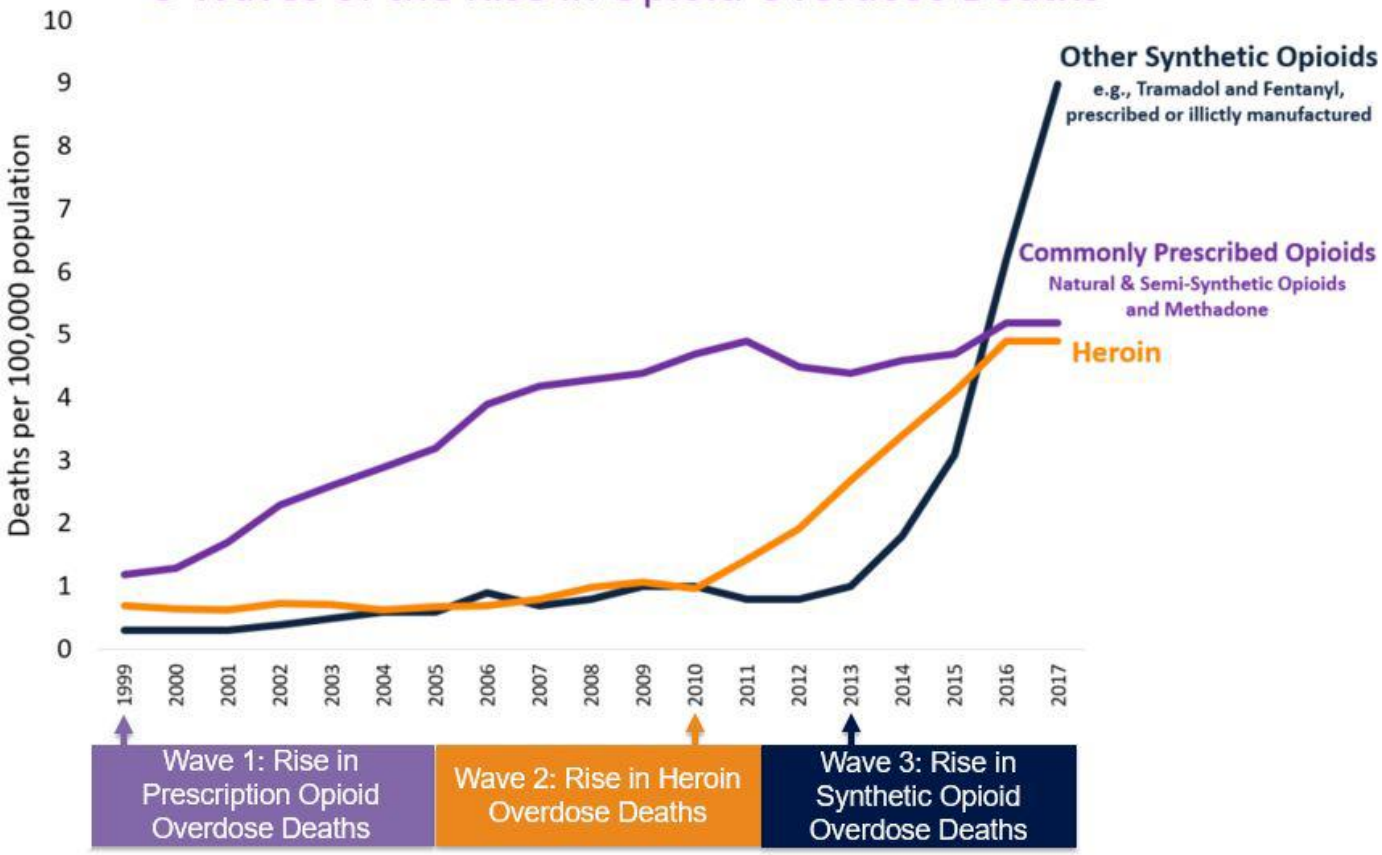
3 Waves of the Rise in Opioid Overdose Deaths



SOURCE: National Vital Statistics System Mortality File.

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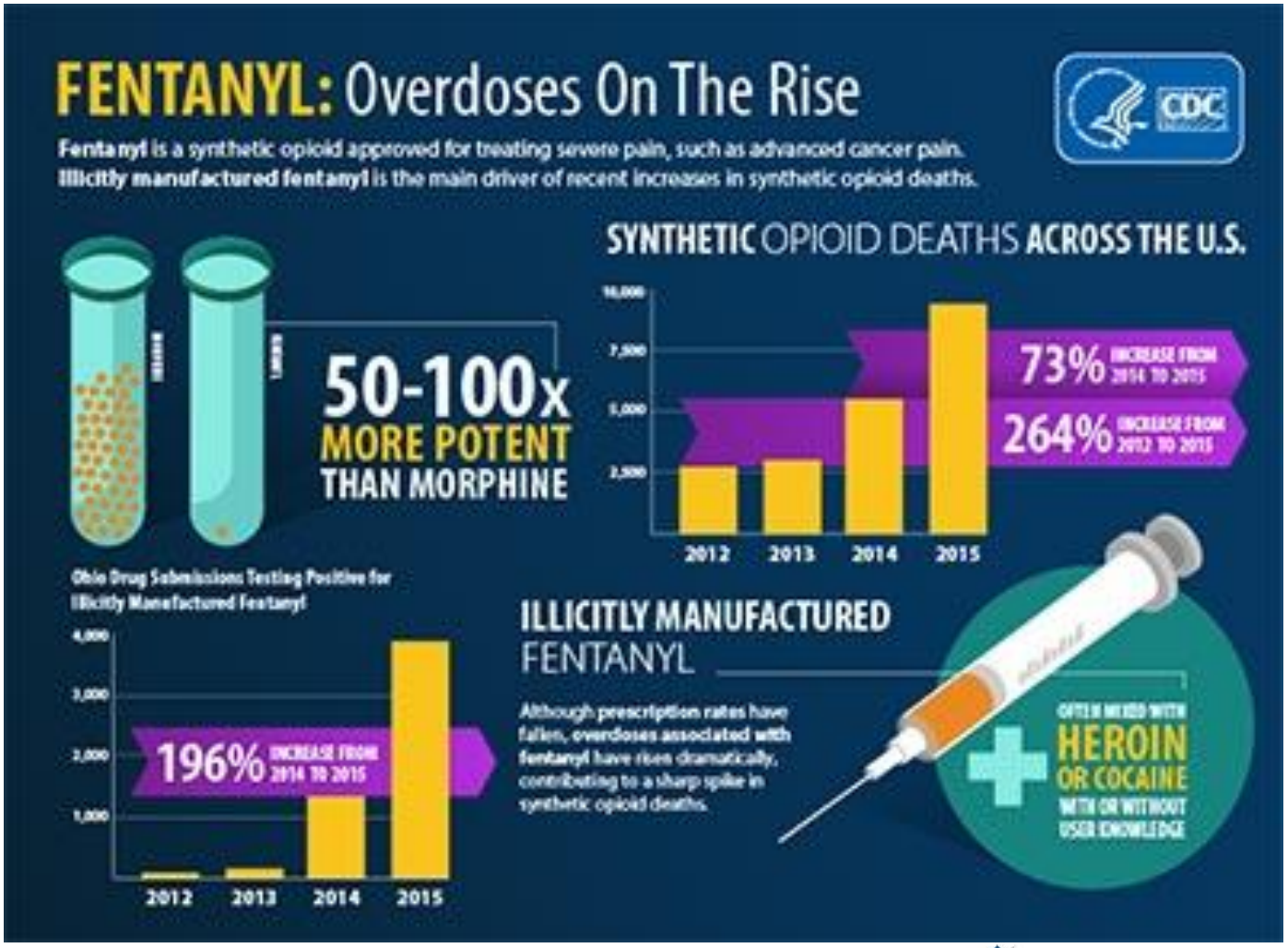
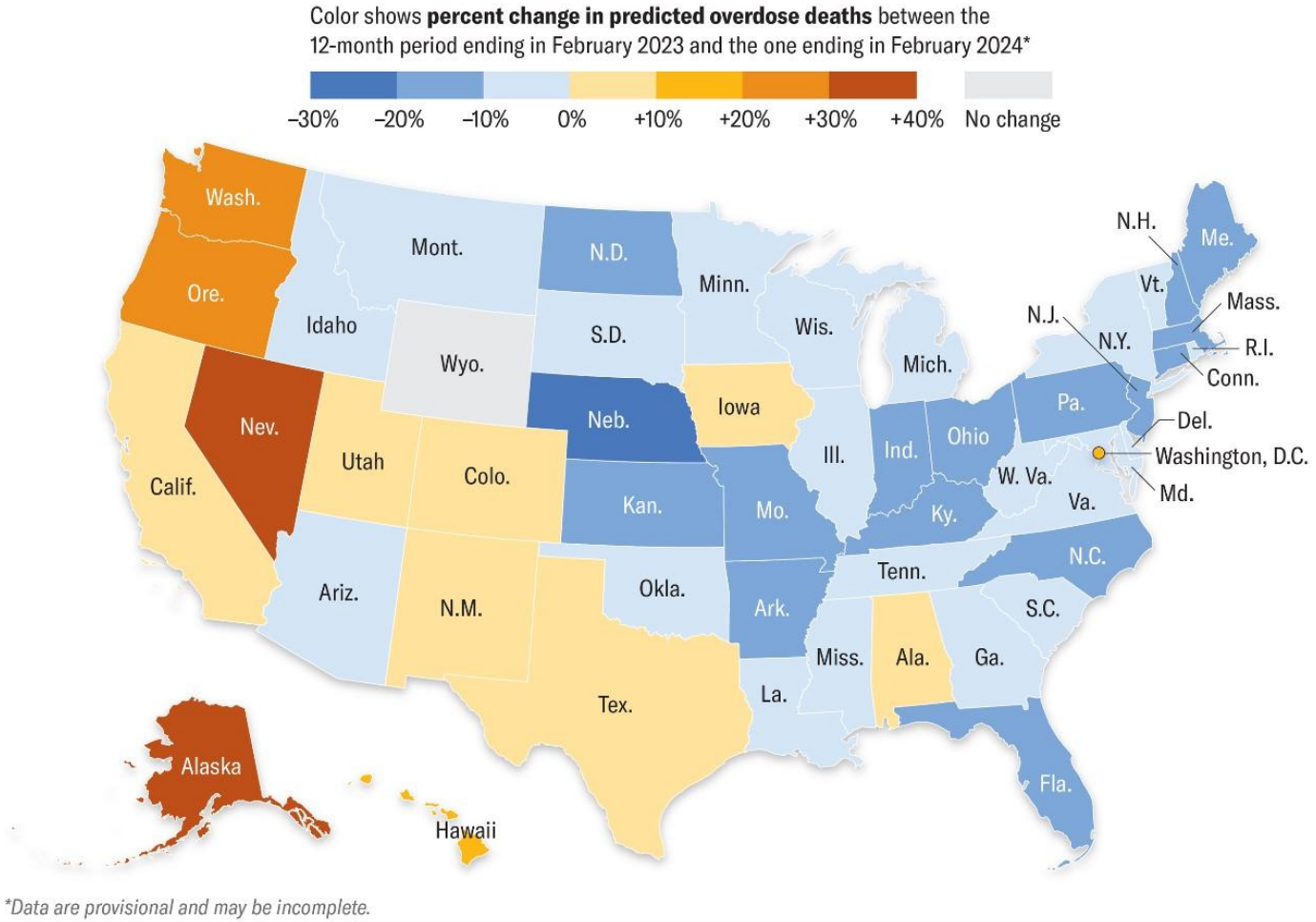

FENTANYL: Overdoses On The Rise
Fentanyl is a synthetic opioid approved for treating severe pain, such as advanced cancer pain.
Illicitly manufactured fentanyl is the main driver of recent increases in synthetic opioid deaths.
CDC
50-100x
MORE POTENT
THAN MORPHINE
SYNTHETIC OPIOID DEATHS ACROSS THE U.S.
73% INCREASE FROM 2014 TO 2015
264% INCREASE FROM 2012 TO 2015
2012
2013
2014
2015
Ohio Drug Submissions Testing Positive for Illicitly Manufactured Fentanyl
196% INCREASE FROM 2014 TO 2015
2012
2013
2014
2015
ILLICITLY MANUFACTURED
FENTANYL
Although prescription rates have fallen, overdoses associated with fentanyl have risen dramatically, contributing to a sharp spike in synthetic opioid deaths.
OFTEN MIXED WITH
HEROIN
OR COCAINE
WITH OR WITHOUT
USER KNOWLEDGE

National Statistics



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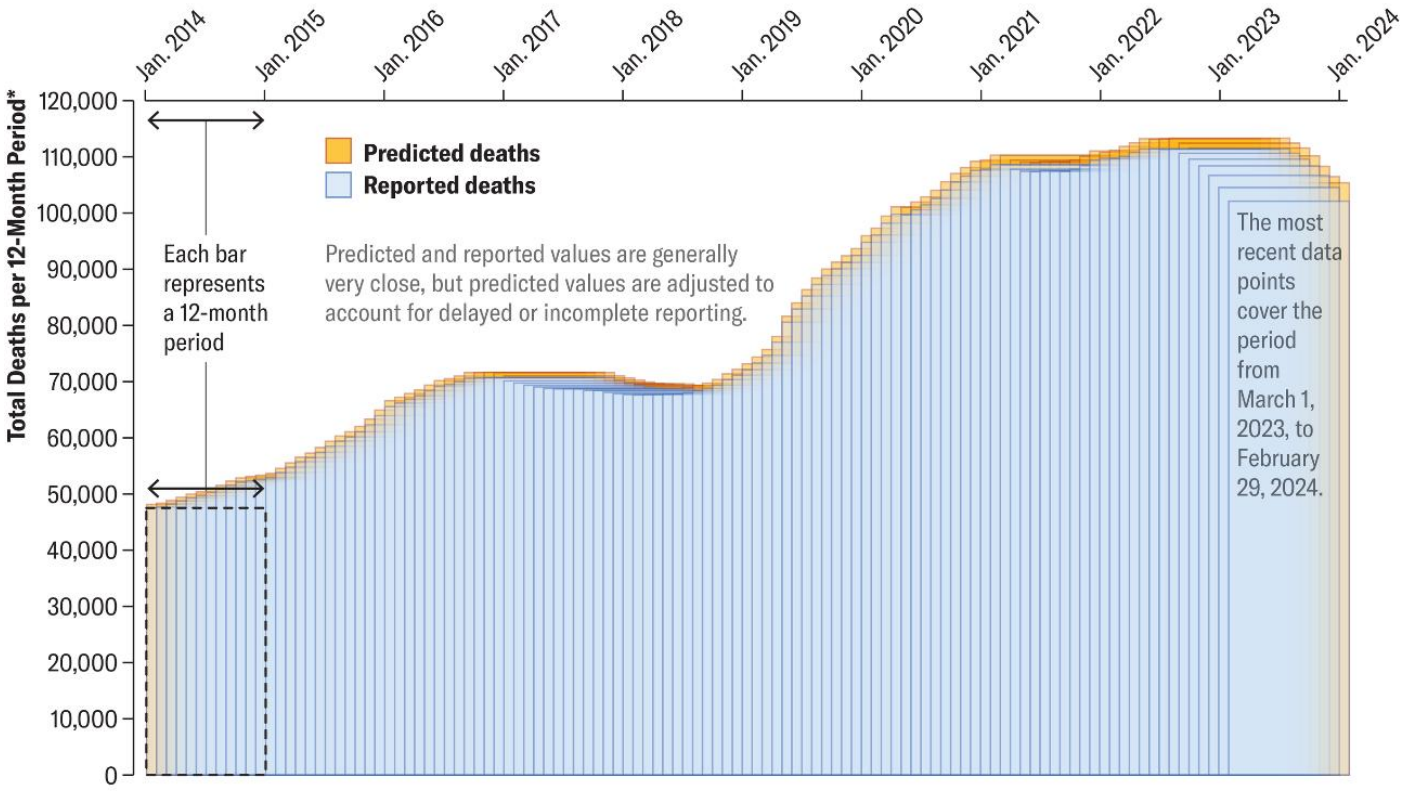
National Statistics

Trends in U.S. Drug Overdose Deaths over the Past Decade

The chart shows how the annual number of deaths caused by drug overdoses has changed in the past 10 years. Each line represents one year's worth of data: the 12-month period ending in a given month. This type of measurement is useful because it cancels out some of the seasonal and other short-term fluctuations that can obscure overall trends.



*Data are provisional and may be incomplete.

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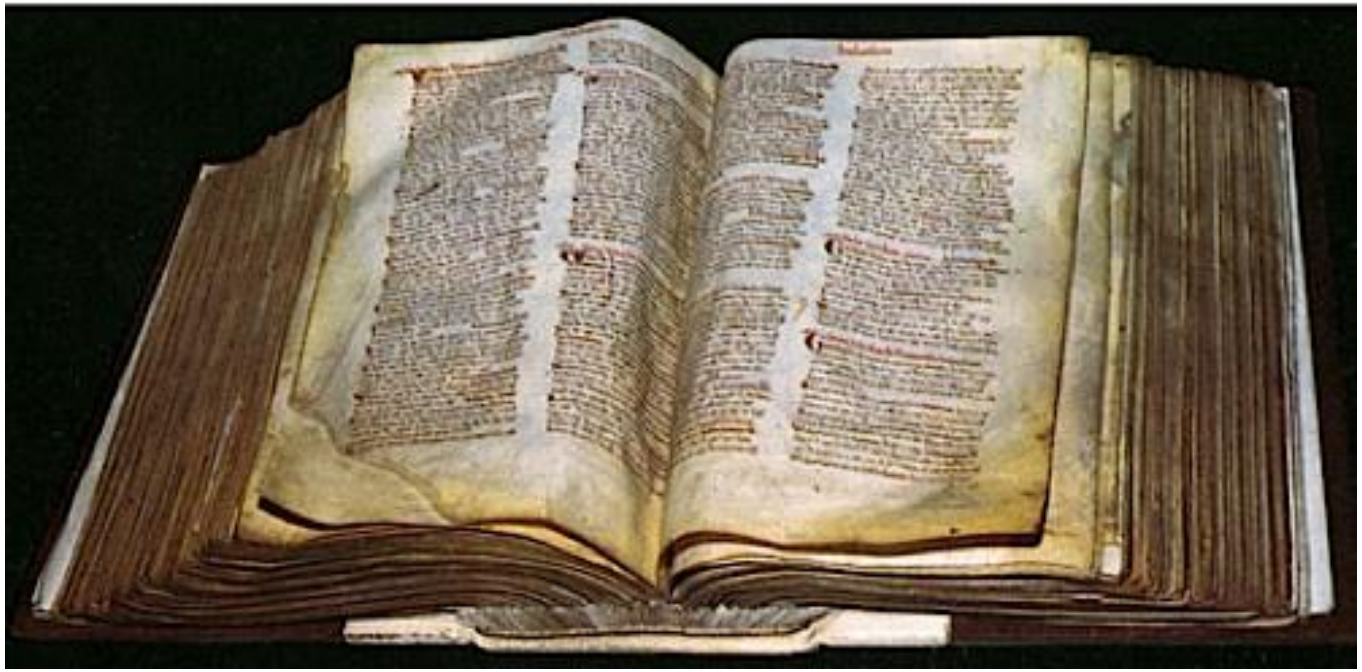
Possible Reasons for reduction in OD deaths

- Potential users have passed away
- Younger generation trending away from lethal fentanyl to other less lethal options
- Reduction in prescribing of opioid pain medication in general
- Higher access to MOUD, mainly buprenorphine

Historical Perspectives



Mid to Late 1800's

- Laudanum used for food poisoning and other GI problems
- Tincture opium used often for people with mild addiction to opioids
- Mostly associated the problem with lower social classes
- Risks from the above were thought to be minimal
- *Commercial morphine production began in 1832 and revolutionized pain treatment*

- Morphine dependence syndrome recognized in civil war veterans given long term morphine for pain control
  (Soldier's disease)

- Soldiers maintained on morphine for OUD treatment

- Crude opium use started to decline by 1887

- Diacetylmorphine commercially available in 1898

- *Medical treatment model switched to "moral and criminal justice model"*

- Opioid use was thought to be due to lack of character and weak morals
- Gradual dose reduction (detoxification) was thought to be “the cure”
- High relapse rates from initial detox trials in Germany
- Similar outcomes reported elsewhere in England

- **Early to mid-1900's**
  - Morphine maintenance clinics opened in early 1900's
  - Daily injections, some by law enforcement officers
  - Continued use of non-patented medicines with opium extracts and cocaine with minimal regulation
  - Importation of opium finally banned in 1909

- **Harrison Narcotics Act (1914)**

  -Established the FDA

  -Made it **illegal** to prescribe opioids for treatment of opioid use disorder

  -Closure of all 44 morphine maintenance clinics in the U.S.

  --~3000 physicians jailed for prescribing opioids for OUD

  -Heroin continued to worsen opioid use

Changing tides

- **Methadone maintenance treatment**
  - Vincent Dole at Rockefeller Institute (now, The Rockefeller University) and Marie Nyswander published study on methadone maintenance in 1965
  - FDA issued regulation in 1972 reversing some elements of Harrison Narcotics Act and legalizing methadone treatment
  - Very heavily federally regulated and outside conventional medical practice
  - Despite evidence of efficacy, never fully accepted as OUD treatment by the majority of medical communities

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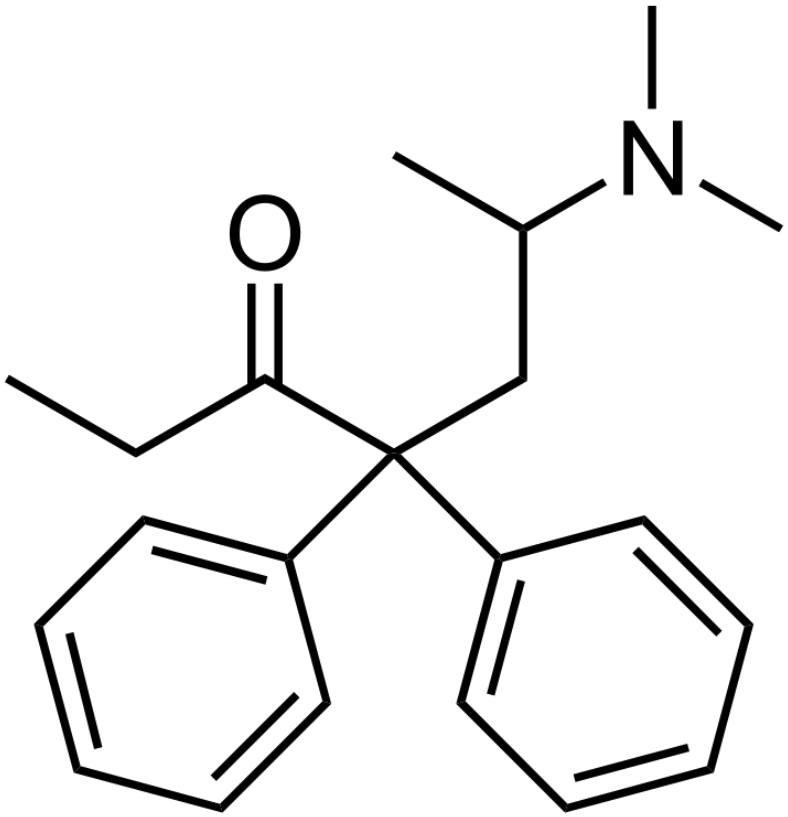
METHADONE



Methadone

- Synthetic, long acting **μ-opioid receptor agonist**
- Racemic mixture of two enantiomers (R- and S-), with R-methadone possessing **10× the affinity for the μ-opioid receptor**
- In vitro, antagonizes the N-methyl-D-aspartate (NMDA) receptor
- Liquid and pill methadone formulations reach maximal plasma concentration in 2 and 3 h, respectively.

Methadone

- **Known adverse effects**

  ≠Significant respiratory depression

  ≠Risk of physiological dependence

  ≠Cardiotoxicity

  ≠QTc prolongation (via blockade of currents through the human ***ether-a-go-go-related gene*** **(hERG)** potassium rectifier channel (IKr)

  ≠Sensorineural hearing loss

  ≠Hypoglycemia

Methadone as MAT

- The **World Health Organization (WHO)** considers methadone an essential medication

- **Cochrane Review (2014) Mattick, et al.** found methadone to be superior to buprenorphine in retaining people in treatment, and methadone equally suppresses illicit opioid use

- Methadone treatment associated with reduced mortality, criminal behavior, and HIV seroconversion

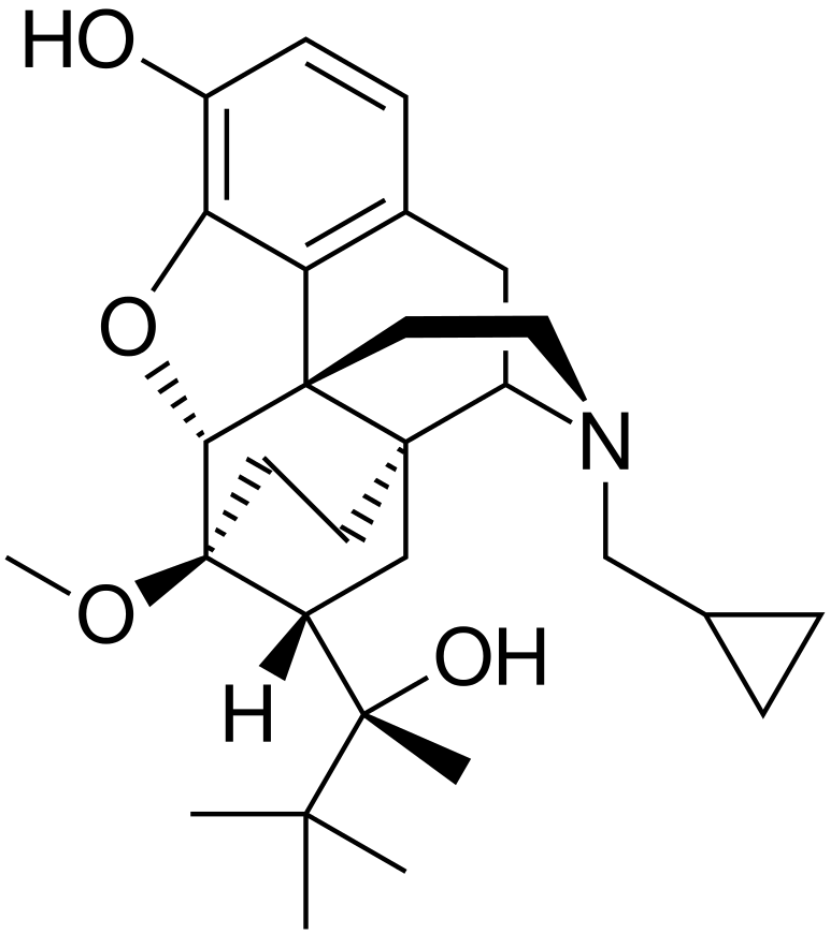
Methadone

- **Practical considerations**
  - ➢Schedule II
  - ➢Only available at federally certified OTPs and acute IP hospital setting for OUD treatment and Pain Clinics at lower dosages
  - ➢Typically requires daily dosing with possibility of take home doses
  - ➢Longer lengths of stay in methadone treatment associated with superior treatment
  - ➢Outcomes
  - ➢Leaving methadone treatment associated with increased risk of death from overdose and other causes
  - ➢Patients should continue as long as they benefit, want to, and develop no contraindications

Role of Methadone in OIH

- Mixed data
- The weak NMDA antagonism appears to show some improvement in OIH
- However, data from patients with long history of OUD shows it can also worsen OIH
- Due to the complex imbalance of pro-nociceptor and anti-nociceptor pathways that occurs in OIH especially in the context of methadone which works both as an opioid agonist and NMDA antagonist

BUPRENORPHINE



Buprenorphine (or Bup/naloxone)

- Semisynthetic, **μ-opioid receptor partial agonist**
- Indicated for the treatment of opioid dependence since 2002 in the US
- Very high binding affinity for the μ-opioid receptor (**more than 1000 times that of morphine**)
- Also binds to the κ- and δ-opioid receptors, albeit with lower affinity

Buprenorphine (or Bup/naloxone)

- **PK/PD**
  - Sublingual bioavailability of BUP is approximately 30%
  - Rapid absorption producing a peak plasma concentration <1 h
  - Long half-life (mean ~ 37 h)
  - Metabolized to **norbuprenorphine**, its major metabolite
  - Via cytochrome P450 **CYP3A4**
  - Glucuronidated and excreted in the feces and urine

Buprenorphine (or Bup/naloxone)

- **Important considerations**
  - Buprenorphine is frequently co-formulated with naloxone, a μ-opioid receptor antagonist, which serves as a deterrent to intravenous (IV) abuse of the medication
  - Due to its high binding affinity and ability to displace many full opioid receptor agonists, administration of BUP to individuals actively using opioids can precipitate opioid withdrawal
  - Patients must be in moderate withdrawal (>8-10 score on COWS) before BUP can be administered and can be titrated based on the symptoms, with maximum dose not to exceed 8 mg on first day

Buprenorphine (or Bup/naloxone)

- **Known adverse effects**

  ≠Risk of physiological dependence

  ≠Overall rate of illicit BUP use among the IV drug using community is rare

  ≠Majority of users reporting use of BUP to manage withdrawal symptoms as opposed to seeking an euphoric effect

  ≠Constipation, nausea, excessive sweating, insomnia, and peripheral edema

  ≠Respiratory depression (**especially when combined with benzos**)

- Buprenorphine treatment associated with significantly reduced inpatient utilization (**81.8% reduction** in hospitalizations vs 43.1% reduction in the no-treatment group)

  Kessel J, et al. Am J Pharm Benefits. 2018;10(1):84-89

- Has outcomes similar to methadone with moderate to high fixed-dose schedules and is highly superior to placebo

- Relatively safe as compared to methadone with ceiling effect on respiratory depression, and less chances of abuse

- Has led to increased access to MOUD and preventing negative outcomes from prolonged opioid use, including in criminal justice settings

Buprenorphine (or Bup/naloxone)

- **Practical considerations**
  - Schedule III
  - Can be prescribed from an outpatient doctor's office
  - **NO DATA2000 waiver requirement since December 2022**
  - Generic Suboxone available since June 2018
  - Home inductions are now the norm with established safety and reliability
  - Depot SC formulation, SUBLOCADE, has been available since 2018

Sublocade

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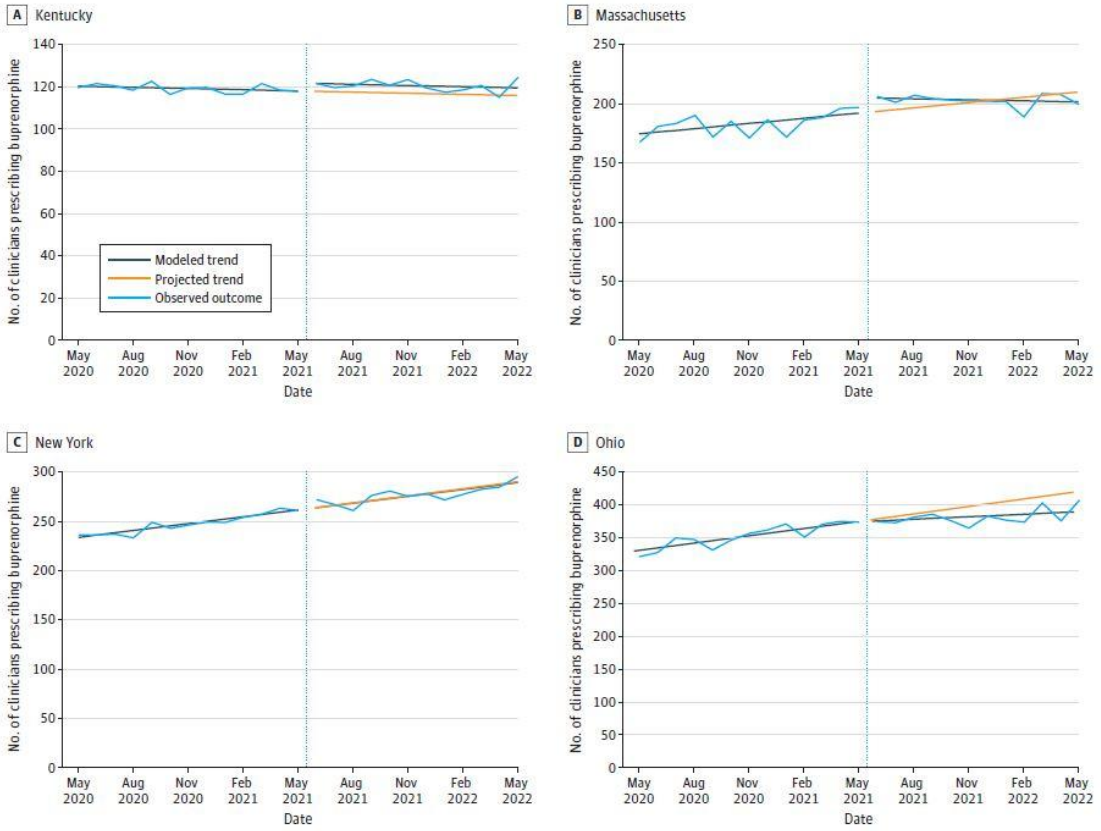
Removal of x-waiver and changes

Figure 2. Number of X-Waivered Clinicians Prescribing Buprenorphine Before and After Relaxation of the X-Waiver Training Requirements, May 2020 to May 2022



Dotted vertical lines indicate the time of the X-waiver training relaxation. Projected trends are based on preperiod data. Modeled trend lines show the outcome accounting for level and linear trend changes due to the X-waiver training relaxation.

Reasons for low BUP prescribing

- DEA audits
- Onerous state requirements
- Inadequate clinical support and/or provider experience
- Insurance requirements such as prior authorizations

Role of Buprenorphine in OIH

- Study by Koppert et al. examined the effects of both sublingual and intravenous buprenorphine in hyperalgesia in a randomized controlled trial.
- Results showed positive anti-hyperalgesic properties of buprenorphine.
- This is due to the buprenorphine-induced antinociception mechanism hypothesis
- Buprenorphine is a κ-receptor antagonist and can compete with the effect of **spinal dynorphin (SD)**, an endogenous κ-receptor agonist.

Role of Buprenorphine in OIH

- Recent case report by Greenhouse et al, shows resolution of OIH with successful initiation of Sublocade
- Another study by Schellekens et al, measuring COMM (Current Opioid Misuse Measurement) scores, showed significant reduction in OIH, pain control, and other measures with opioid rotation to buprenorphine in patients with OUD in inpatient settings
- More such studies showing efficacies ranging from moderate to highly effective
- **However**, this is not FDA approved for this purpose and more data is needed.

Patient status currently

- Treatment plan:
  - » Opioid taper schedule started
  - » Provided with individual therapy with focus on coping skills
  - » MOUD with buprenorphine was initiated with transition to maintenance
  - » Referral made to Integrative Clinic for PT and alternative pain reduction techniques

Patient status currently

- Patient completely abstaining from licit and illicit opioids
- Reports improvement in her pain perception with reduction in overall pain
- She is maintained on buprenorphine-naloxone 8-2 mg SL TID
- Continues to remain compliant with treatment currently.

Take Home Points

- Opioid Induced Hyperalgesia is a known concern which is frequently seen in patients with chronic pain
- Approach patients with OIH by rotating opioid pain medications, lowering the dosages, and considering transition to multimodal techniques
- Consider transition of high dose opioid patients for MOUD treatment such as buprenorphine which reduces sensitization and alleviates OIH
- More studies needed, especially more robust human trials data in future.

References

- Wilson SH, Hellman KM, James D, Adler AC, Chandrakantan A. Mechanisms, diagnosis, prevention and management of perioperative opioid-induced hyperalgesia. Pain Manag. 2021 Apr;11(4):405-417. doi: 10.2217/pmt-2020-0105. Epub 2021 Mar 29. PMID: 33779215; PMCID: PMC8023328.

- Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. Pain Physician. 2011 Mar-Apr;14(2):145-61. PMID: 21412369.

- American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.)

- Podvin S, Yaksh T, Hook V. The Emerging Role of Spinal Dynorphin in Chronic Pain: A Therapeutic Perspective. Annu Rev Pharmacol Toxicol. 2016;56:511-33. doi: 10.1146/annurev-pharmtox-010715-103042. PMID: 26738478; PMCID: PMC4902163.

- Koppert W, Ihmsen H, Körber N, Wehrfritz A, Sittl R, Schmelz M, Schüttler J. Different profiles of buprenorphine-induced analgesia and antihyperalgesia in a human pain model. Pain. 2005 Nov;118(1-2):15-22. doi: 10.1016/j.pain.2005.06.030. Epub 2005 Sep 9. PMID: 16154698.

- Schellekens AFA, Veldman SE, Suranto ESD, van Rijswijk SM, van der Wal SEI, Schene AH, van Beek MHCT. Beneficial Effects of Opioid Rotation to Buprenorphine/Naloxone on Opioid Misuse, Craving, Mental Health, and Pain Control in Chronic Non-Cancer Pain Patients with Opioid Use Disorder. Journal of Clinical Medicine. 2021; 10(16):3727. https://doi.org/10.3390/jcm10163727

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