Opioid Use Disorder

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Disclosure

I have NO financial disclosure or conflicts of interest with the presented material in this presentation.

Learning Outcomes

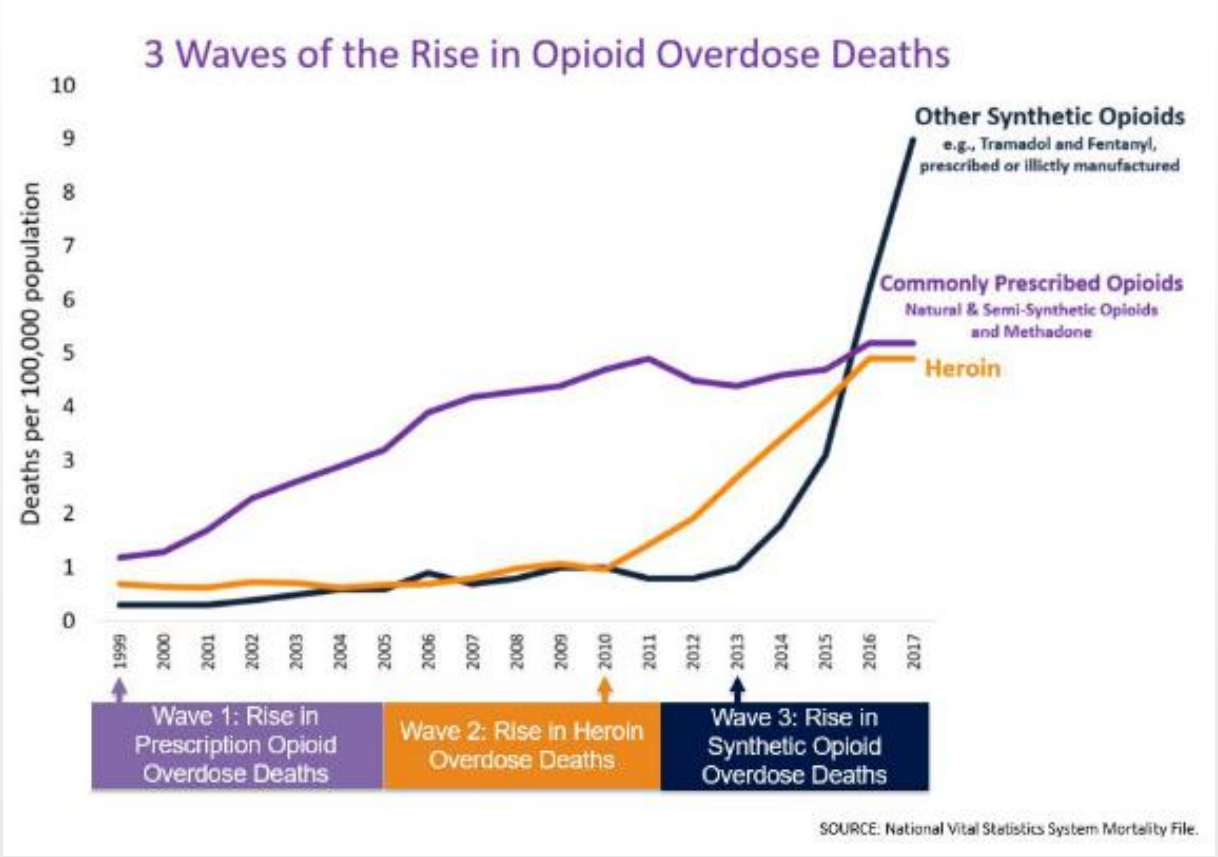
Upon completion of this topic, the listener should be able to do the following:

- Describe the genesis of today's opioid epidemic.
- Explain how opioids cause reward, reinforcement, and dependence.
- Discuss different approaches to the treatment of opioid use disorder.

Genesis of the Opioid Epidemic

- OxyContin® (oxycodone) was introduced by Purdue Pharma in 1995 and was aggressively marketed as a safe, long-lasting opioid with very low potential for abuse.
- The company disseminated misinformation that opioids should be prescribed for the treatment of all sorts of pain because there was a less-than-1% risk of addiction.
- An aggressive marketing strategy included all-expenses-paid symposia for healthcare professionals and their families, and recruitment of candidates for training for Purdue's speaker bureau to propagate the misinformation about opioids.

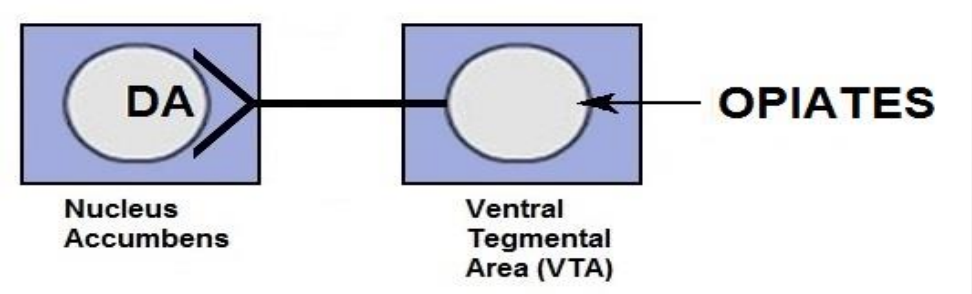
As sales of prescription opioids increased between 1999 and 2016, so too did the number of opioid-related fatalities.


3 Waves of the Rise in Opioid Overdose Deaths
Deaths per 100,000 population
0
1
2
3
4
5
6
7
8
9
10
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
Other Synthetic Opioids
e.g., Tramadol and Fentanyl, prescribed or illictly manufactured
Commonly Prescribed Opioids
Natural & Semi-Synthetic Opioids and Methadone
Heroin
Wave 1: Rise in Prescription Opioid Overdose Deaths
Wave 2: Rise in Heroin Overdose Deaths
Wave 3: Rise in Synthetic Opioid Overdose Deaths
SOURCE: National Vital Statistics System Mortality File.

Purdue Pharma

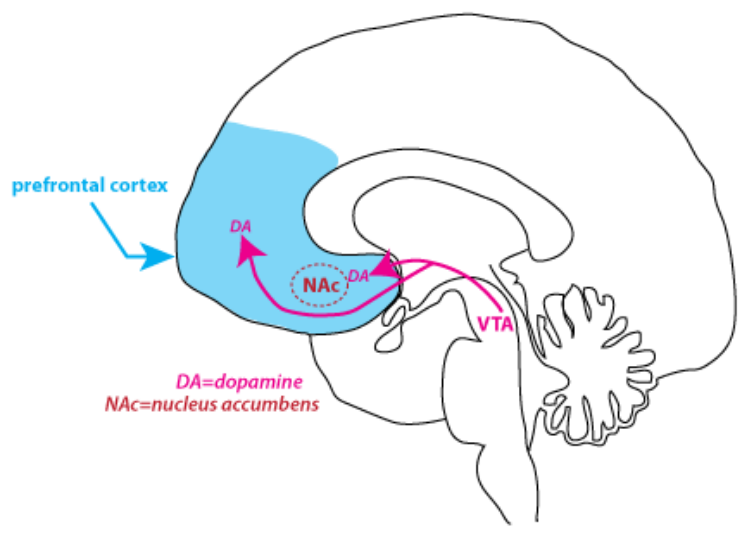
- In 2007, Purdue Pharma, the manufacturer of OxyContin®, pleaded guilty to misleading the medical community and public about its risk of addiction. The company was fined $600 million, and three top company officials were fined a total of $34.5 million.
- By 2019, there were over one thousand lawsuits against Purdue Pharma filed by states, cities, counties, and Native American reservations for over $2 trillion. Purdue filed for bankruptcy and is providing billions in some settlements.
- The owners of Purdue Pharma, the Sackler family, are seeking immunity from civil lawsuits. It will be decided by the Supreme Court.

How Are Opiates Addictive?



- Opiates cause release of dopamine (DA) from VTA neurons that innervate neurons in the nucleus accumbens, the reward center.
- Addictive drugs provide a shortcut to the brain's reward system by flooding the nucleus accumbens with dopamine.
  - The hippocampus lays down memories of this rapid sense of satisfaction, and the amygdala creates a conditioned response to certain stimuli.

The Reward Circuit

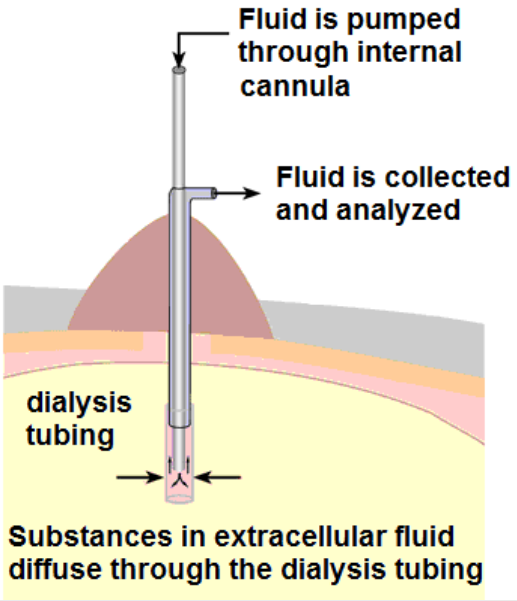


The reward circuit is complex, but it contains a central link that plays a fundamental role.

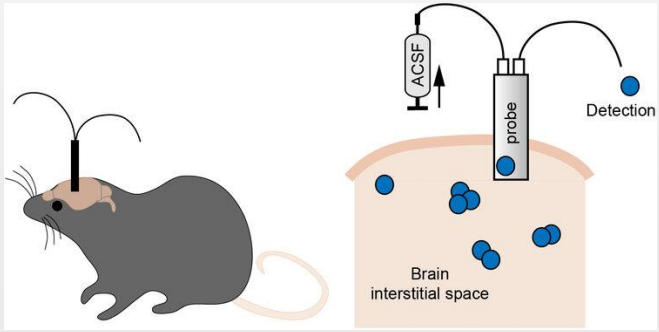
This link consists of the nerve connections between two particular small groups of neurons.

- ventral tegmental area (VTA)
- nucleus accumbens

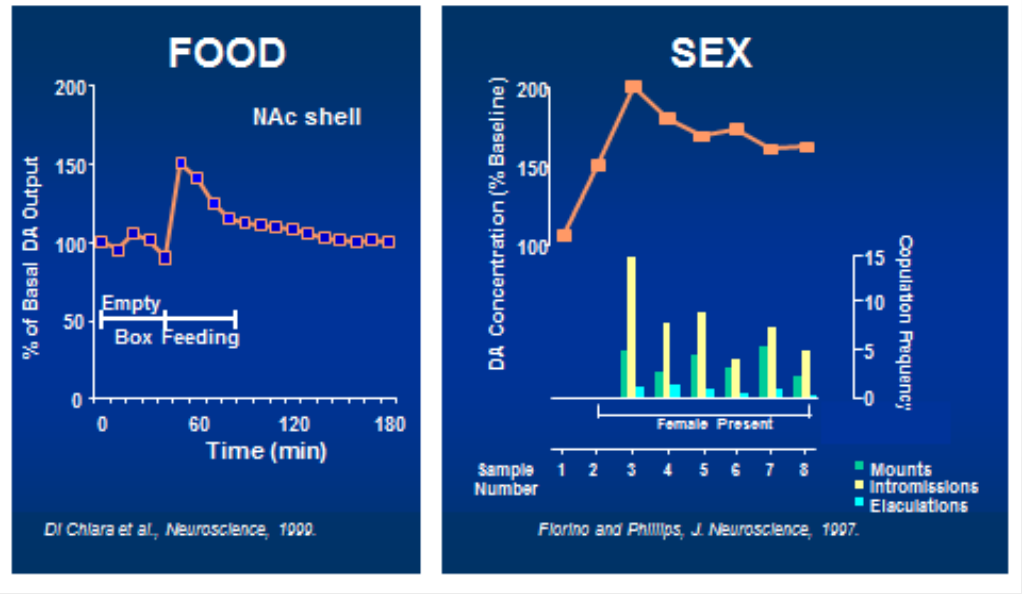
MICRODIALYSIS



Microdialysis is a sampling technique used for continuous measurement of small molecular weight substances in the extracellular fluid of tissues.

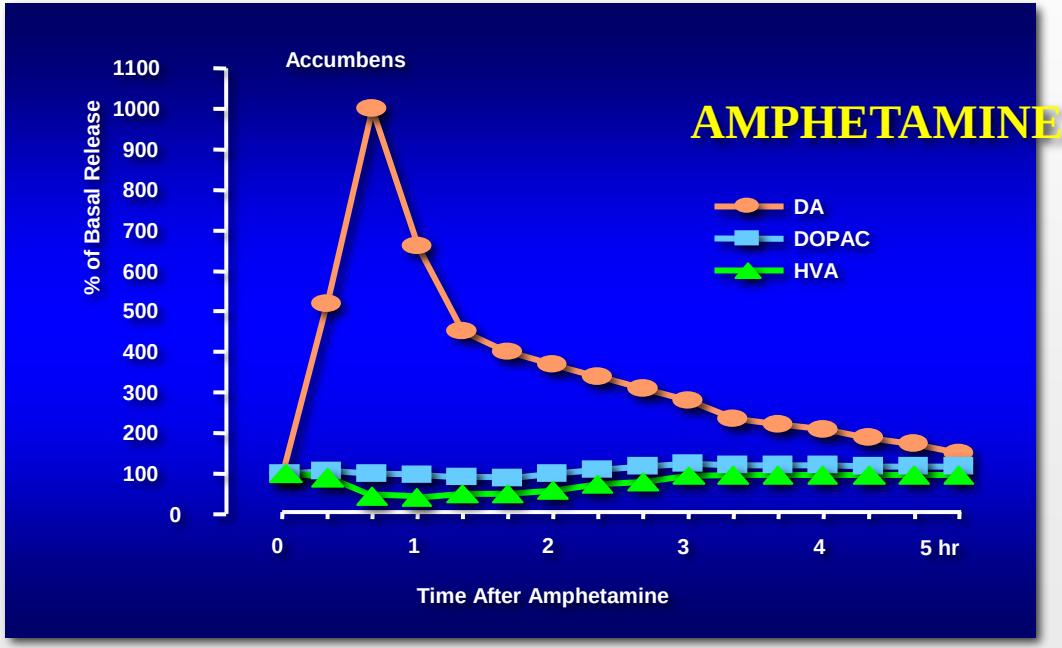


Natural Rewards

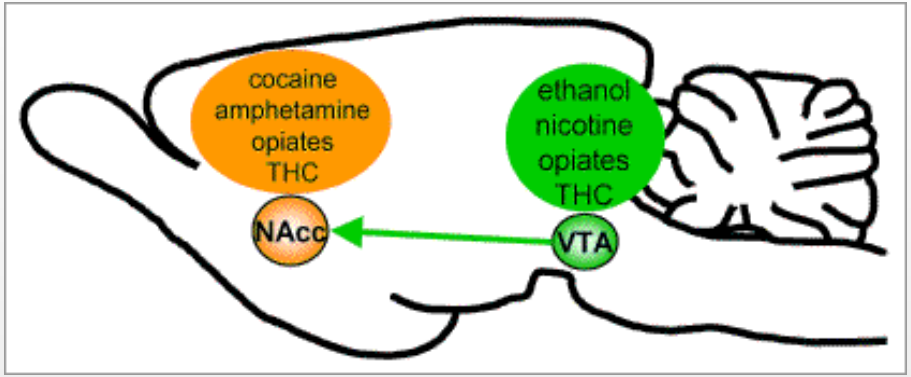


Natural rewards (*e.g.*, food, sexual activity) stimulate ventral tegmental area neurons to release dopamine and activate DA receptors in the nucleus accumbens.

Drug Rewards



Addictive Drugs



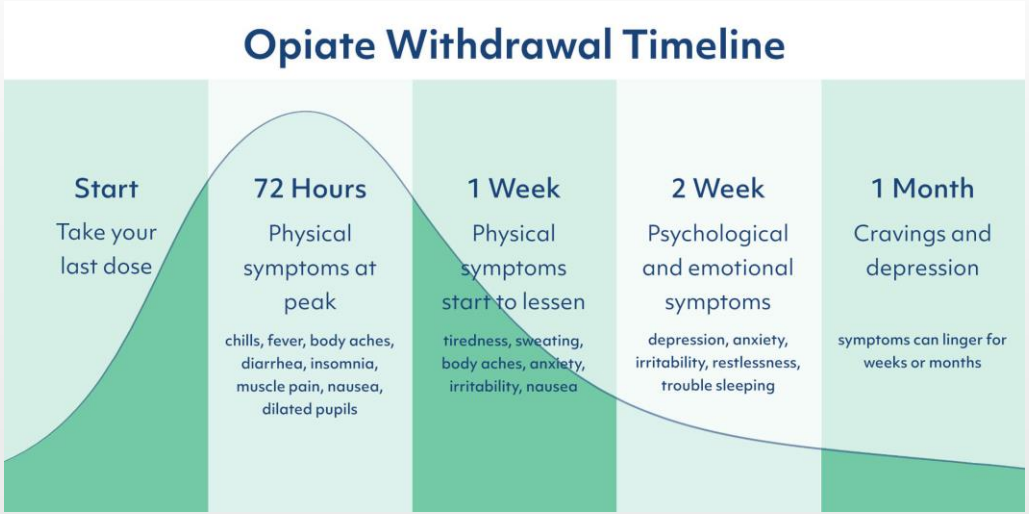
- Many drugs of abuse produce even greater neuronal release of dopamine as well as changes in other brain regions.
- Drugs that produce the greatest elevations in brain dopamine tend to be more addictive.

Drug Addiction

- Opioid drugs with high abuse potential tend to induce compulsive drug-seeking behavior.
- The persistent drug-seeking behavior of dependent individuals is maintained by the reinforcing properties of the drug. This activity continues despite its negative social, psychological, and physical consequences.
- Preoccupation with obtaining and using the drug may so demanding as to decrease the user's productivity.
- There is a high tendency to relapse in drug addicts.

Opioid Withdrawal

- Repeated doses of opioids quickly lead to tolerance and dependence.
- Sudden cessation of opioid use or reduction of dose results in significant signs of withdrawal.



Opioid Withdrawal Signs

OPIOID DRUG EFFECT	OPIOID WITHDRAWAL SIGN
Analgesia	Hyperalgesia
Euphoria	Dysphoria
Drowsiness	Insomnia
Miosis	Mydriasis
Hypothermia	Hyperthermia
Bradycardia	Tachycardia
Hypotension	Hypertension
Areflexia	Hyperreflexia
Constipation	Diarrhea

Approaches to Treating Opioid Addiction

- Medications include methadone and buprenorphine, both of which work by binding to the same cell receptors as heroin but more weakly or with reduced efficacy, helping a person to wean off the drug and reduce craving.
- Behavioral therapies can include contingency management therapy and cognitive-behavioral intervention.

Methadone

- Methadone is a synthetic opioid drug with properties similar to those of morphine and other opioid drugs.
- Methadone is used to reduce and, hopefully, eliminate heroin use by stabilizing people struggling with addiction for as long as necessary to avoid returning to earlier patterns of drug use.

Methadone (Dolophine®)

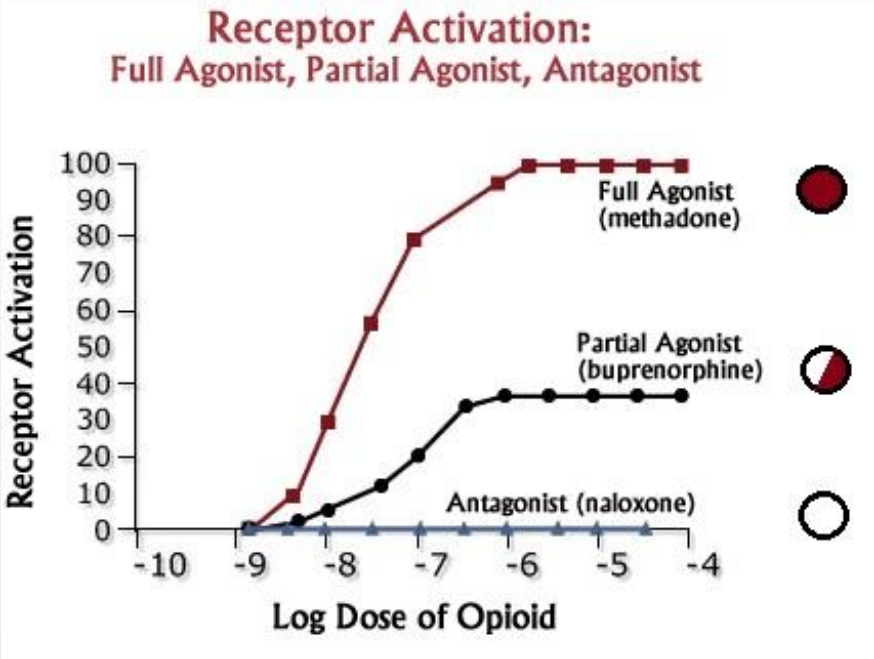
Advantages of methadone

- taken orally, slower acting than injected heroin (30 min *vs.* immediate)

  - does not cause a "high" or drowsiness
  - does not impair thinking, behavior, or functioning
  - does not dull normal emotions and physical sensations

- longer-acting than heroin (24-36 hr *vs.* 3-6 hr) and is administered less often (once a day *vs.* 3-4 daily)
- suppresses heroin withdrawal

Methadone *vs.* Buprenorphine *vs.* Naloxone



Buprenorphine and Naloxone

- The combination of buprenorphine and naloxone is marketed as Suboxone®. Buprenorphine is a weak opioid agonist that acts at opioid receptors, while naloxone is an opioid antagonist that blocks opioid receptors.
- The bioavailability of naloxone when Suboxone® is taken orally is minimal. If Suboxone® is crushed and injected, the bioavailability of naloxone dramatically increases, and it acts as an antagonist.

Naltrexone

- Long-acting and potent antagonist of opioid receptors
- Binds to and blocks opioid receptors to prevent the euphoric and sedative effects of opioids.
- There is no abuse and diversion potential with naltrexone.

Preclinical Study

Contents lists available at ScienceDirect

Brain Research

journal homepage: www.elsevier.com/locate/brainres

Hyperbaric oxygen treatment suppresses withdrawal signs in morphine-dependent mice

Daniel Nicoara [a,1], Yangmiao Zhang [b,2], Jordan T. Nelson [a,3], Abigail L. Brewer [a], Prianka Maharaj [b], Shea N. DeWald [a], Donald Y. Shirachi [d], Raymond M. Quock [a,b,c,*]

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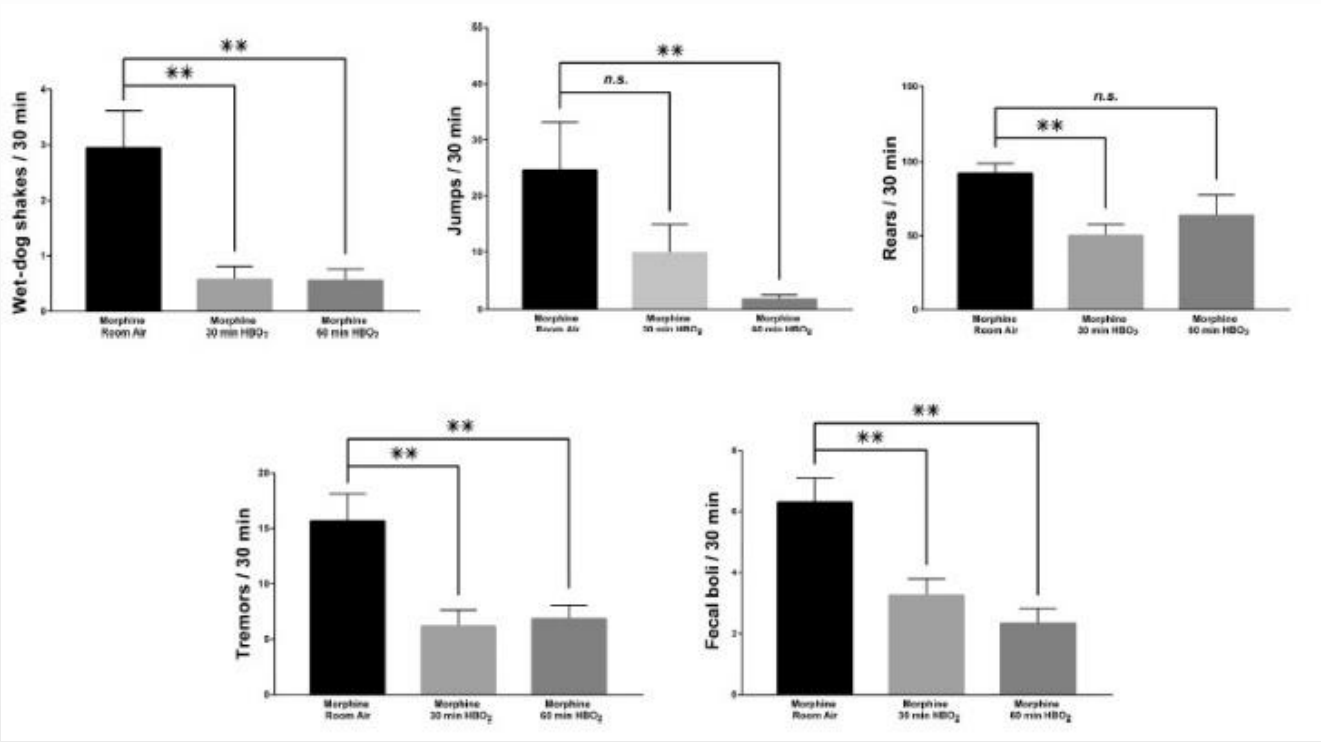
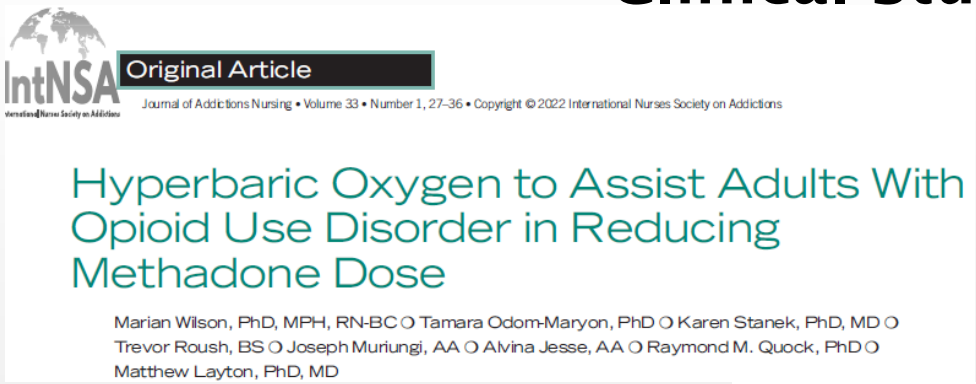


Nicoara *et al.,* Hyperbaric oxygen treatment suppresses withdrawal signs in morphine-dependent mice. *Brain Research* 1648:434-437, 2016

Clinical Studies



IntNSA Original Article

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Hyperbaric Oxygen to Assist Adults With Opioid Use Disorder in Reducing Methadone Dose

Marian Wilson, PhD, MPH, RN-BC ○ Tamara Odom-Maryon, PhD ○ Karen Stanek, PhD, MD ○ Trevor Roush, BS ○ Joseph Muriungi, AA ○ Alvina Jesse, AA ○ Raymond M. Quock, PhD ○ Matthew Layton, PhD, MD

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***Pain Management Nursing*, Vol. 23(5), pp. 616-624, 2022**

Contents lists available at ScienceDirect

Pain Management Nursing

journal homepage: www.painmanagementnursing.org

Original Article

Hyperbaric Oxygen Therapy for Pain, Opioid Withdrawal, and Related Symptoms: A Pilot Randomized Controlled Trial

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Summary of Clinical Studies

- Hyperbaric oxygen therapy (HBOT) reduced the intensity of withdrawal symptoms in methadone patients* following a 10% reduction in the daily dose of methadone.
- HBOT caused a sustained reduction in the daily dose of methadone one month after HBOT compared to control.
- HBOT reduced drug craving, pain intensity, depression, and sleep disturbance.
- Study retention and treatment satisfaction were high.

* COWS, Clinical Opioid Withdrawal Scale; ARSQ, Adjective Rating Scale for Withdrawal

Potential Uses of HBOT in the Opioid Epidemic

Opioid Detoxification

- Suppression of opioid withdrawal signs
- Facilitate transfer to medication-assisted treatment (MAT)


QUESTIONS?
WHEN?
WHERE?
WHAT?
WHO?
HOW?
WHY?
Where?
When?
What?

Naltrexone (Vivitrol®)

- Long-acting antagonist prevents opioid receptors from inhibiting ability of GABA interneurons to inhibit dopamine release in the reward center
- Blocks the normal subjective (euphoric and sedative) effects of opioids
- There is no abuse and diversion potential with naltrexone.