
Medications for
Opioid Use Disorders
MUSC Health
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Changing What's Possible | MUSChealth.org
Karen Hartwell MD Associate Professor

No conflicts of interest relevant to today's topic

Opium Poppy (papaver somniferum)

Over 50 botanical varieties with varying alkaloid content

Tears contain 12% morphine

Opium is the dried latex from slit seed capsules

Grows in warm dry climates, majority in 4,500 mile stretch of mountains across central Asia. Now grown in Latin America (mainly Columbia & Mexico).

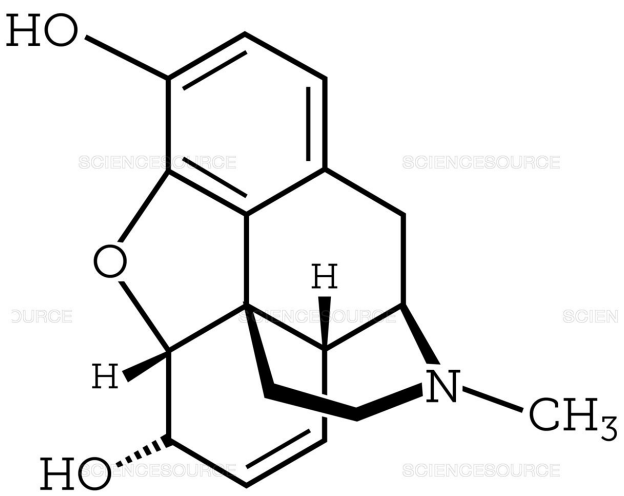
Use of Opium in Ancient Civilizations

- Poppies first cultivated in lower Mesopotamia ≈3400 BC
- Ancient Greeks named the sap *opion*, the origin of the name opium (dried latex from slit poppyseeds, turn into brown gum-like mass)
- Images found in ancient Sumerian (≈ 4000 BC) and Egyptian artifacts
- Cultivation spread to Assyria, Egypt and along the Silk Road to China
- Used for analgesia, sleep, and given relief to the bowels

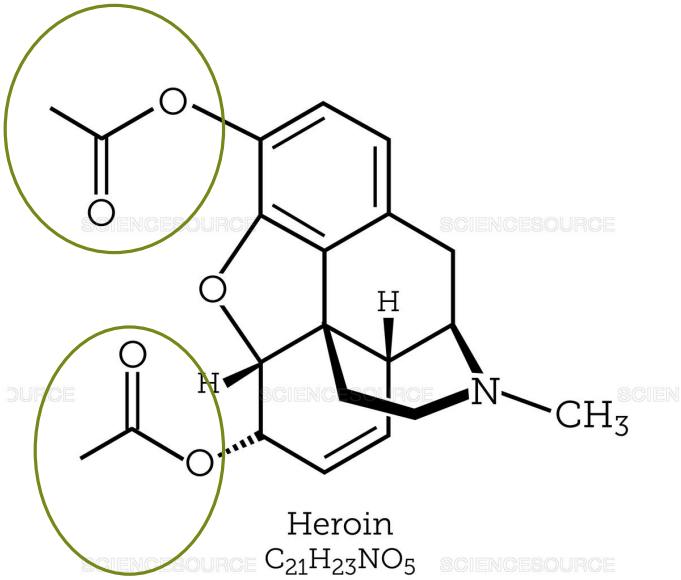
Earrings found in tomb of Queen Taurset

What happened from there?

- In 1600s laudanum (an alcohol tincture of alkaloids) was developed. Available OTC until early 1900s. Prescribed for pain and cough. Victorian women prescribed for menstrual cramps.
- 1803 morphine (from Morpheus, Greek God of dreams) was extracted from the opium resin (10x more potent than processed opium)
- 1840-50s hypodermic syringe developed and used in the American Civil War
- 1874 heroin first synthesized from morphine. Medical use started 1898. By early 1900s heroin abuse had risen to alarming rates.
- 1914 Harrison Act
- **1924 federal law made all distribution and sale of heroin (and opium & cocaine) illegal**



Morphine
$C_{17}H_{19}NO_3$



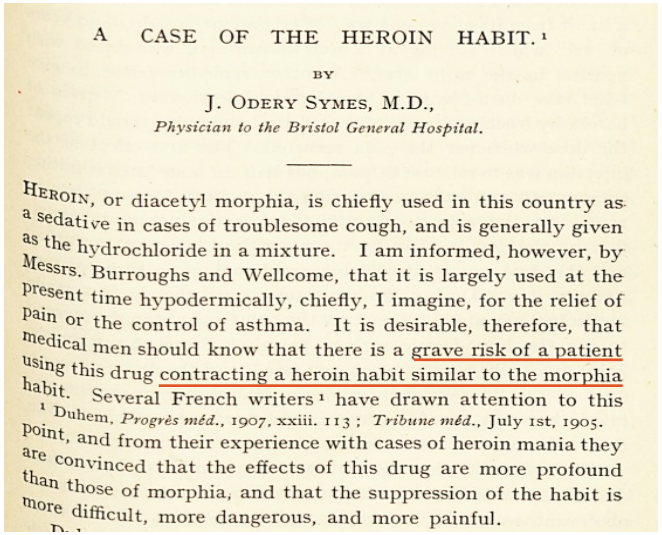
Heroin
$C_{21}H_{23}NO_5$

(diacetylmorphine)

Felix Hoffman, the chemist who created aspirin for Bayer, synthesized heroin in an attempt to convert morphine to codeine. Made by boiling morphine with acetic anhydride. Was thought to be safe non-addictive substitute for morphine.

1910 Bellevue admitted its first case of heroin dependence. 5 years later 425 patients admitted.

Early journal articles



A CASE OF THE HEROIN HABIT.[1]

BY

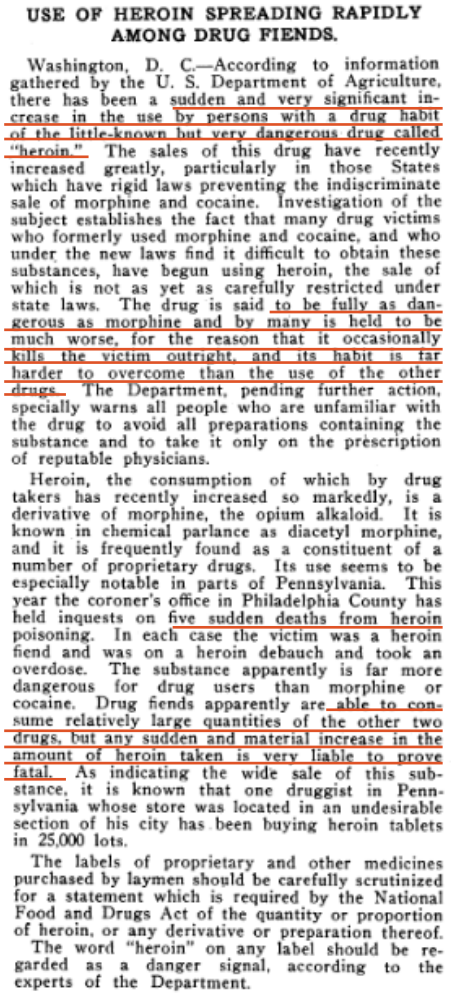
J. ODERY SYMES, M.D.,

Physician to the Bristol General Hospital.

HEROIN, or diacetyl morphia, is chiefly used in this country as a sedative in cases of troublesome cough, and is generally given as the hydrochloride in a mixture. I am informed, however, by Messrs. Burroughs and Wellcome, that it is largely used at the present time hypodermically, chiefly, I imagine, for the relief of pain or the control of asthma. It is desirable, therefore, that medical men should know that there is a grave risk of a patient using this drug contracting a heroin habit similar to the morphia habit. Several French writers[1] have drawn attention to this point, and from their experience with cases of heroin mania they are convinced that the effects of this drug are more profound than those of morphia, and that the suppression of the habit is more difficult, more dangerous, and more painful.

[1] Duhem, *Progrès méd.*, 1907, xxiii. 113; *Tribune méd.*, July 1st, 1905.

Bristol Medico-Chirurgical Journal 1912



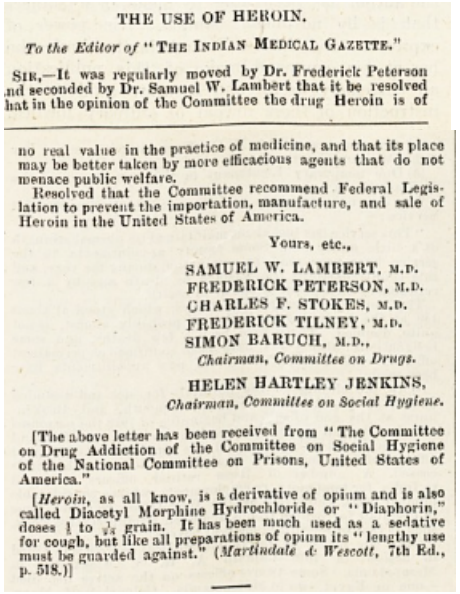
USE OF HEROIN SPREADING RAPIDLY AMONG DRUG FIENDS.

Washington, D. C.—According to information gathered by the U. S. Department of Agriculture, there has been a sudden and very significant increase in the use by persons with a drug habit of the little-known but very dangerous drug called "heroin." The sales of this drug have recently increased greatly, particularly in those States which have rigid laws preventing the indiscriminate sale of morphine and cocaine. Investigation of the subject establishes the fact that many drug victims who formerly used morphine and cocaine, and who under the new laws find it difficult to obtain these substances, have begun using heroin, the sale of which is not as yet as carefully restricted under state laws. The drug is said to be fully as dangerous as morphine and by many is held to be much worse, for the reason that it occasionally kills the victim outright, and its habit is far harder to overcome than the use of the other drugs. The Department, pending further action, specially warns all people who are unfamiliar with the drug to avoid all preparations containing the substance and to take it only on the prescription of reputable physicians.

Heroin, the consumption of which by drug takers has recently increased so markedly, is a derivative of morphine, the opium alkaloid. It is known in chemical parlance as diacetyl morphine, and it is frequently found as a constituent of a number of proprietary drugs. Its use seems to be especially notable in parts of Pennsylvania. This year the coroner's office in Philadelphia County has held inquests on five sudden deaths from heroin poisoning. In each case the victim was a heroin fiend and was on a heroin debauch and took an overdose. The substance apparently is far more dangerous for drug users than morphine or cocaine. Drug fiends apparently are able to consume relatively large quantities of the other two drugs, but any sudden and material increase in the amount of heroin taken is very liable to prove fatal. As indicating the wide sale of this substance, it is known that one druggist in Pennsylvania whose store was located in an undesirable section of his city has been buying heroin tablets in 25,000 lots.

The labels of proprietary and other medicines purchased by laymen should be carefully scrutinized for a statement which is required by the National Food and Drugs Act of the quantity or proportion of heroin, or any derivative or preparation thereof. The word "heroin" on any label should be regarded as a danger signal, according to the experts of the Department.

California State J Med 1914



THE USE OF HEROIN.

To the Editor of "THE INDIAN MEDICAL GAZETTE."

SIR,—It was regularly moved by Dr. Frederick Peterson and seconded by Dr. Samuel W. Lambert that it be resolved that in the opinion of the Committee the drug Heroin is of no real value in the practice of medicine, and that its place may be better taken by more efficacious agents that do not menace public welfare.

Resolved that the Committee recommend Federal Legislation to prevent the importation, manufacture, and sale of Heroin in the United States of America.

Yours, etc.,

SAMUEL W. LAMBERT, M.D.
FREDERICK PETERSON, M.D.
CHARLES F. STOKES, M.D.
FREDERICK TILNEY, M.D.
SIMON BARUCH, M.D.,
Chairman, Committee on Drugs.

HELEN HARTLEY JENKINS,
Chairman, Committee on Social Hygiene.

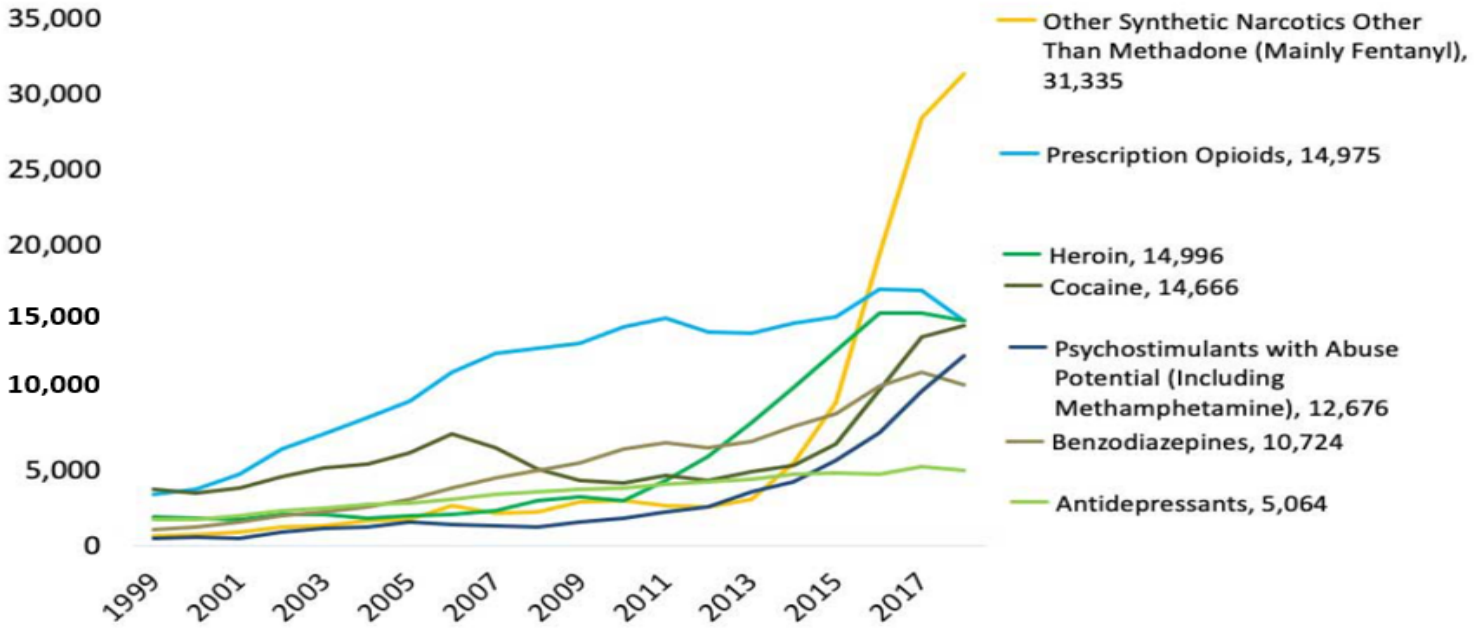
[The above letter has been received from "The Committee on Drug Addiction of the Committee on Social Hygiene of the National Committee on Prisons, United States of America."

[*Heroin*, as all know, is a derivative of opium and is also called Diacetyl Morphine Hydrochloride or "Diaphorin," doses ½ to ¾ grain. It has been much used as a sedative for cough, but like all preparations of opium its "lengthy use must be guarded against." (*Martindale & Wescott*, 7th Ed., p. 518.)]

Indian Medical Gazette 1917

Worsening Epidemic

Figure 2. National Drug Overdose Deaths Number Among All Ages, 1999-2018



Source: : Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2018 on CDC WONDER Online Database, released January, 2019

Opioid Use Disorders

Loss of control	Pharmacological*	Risky Use	Adverse Effects on Functioning
Taken in larger amounts or longer than intended	Tolerance: (1)↑ amts to achieve desire effects (2) ↓ effect with same amount	Use in situations where physically hazardous	Failure to fulfill obligations at home, work, or school
Persistent desire to or unsuccessful efforts to cut down or control use	Withdrawal: (1) opioid withdrawal syndrome (2) taken to relieve to avoid or reduce withdrawal sx	Continued use despite knowledge of physical or psychological problems likely related to substance	Continued use despite persistent or recurrent social or interpersonal problems related to opioid use
Great deal of time obtaining, using, recovering			Impt social, occupational, recreation activities given up or reduced related to use
Craving			

Mild: 2-3 sx
Moderate: 4-5
Severe: 6 or more

***Exception: pharmacological criteria do not apply in presence of chronic opioid therapy**

Opioid Withdrawal

Signs

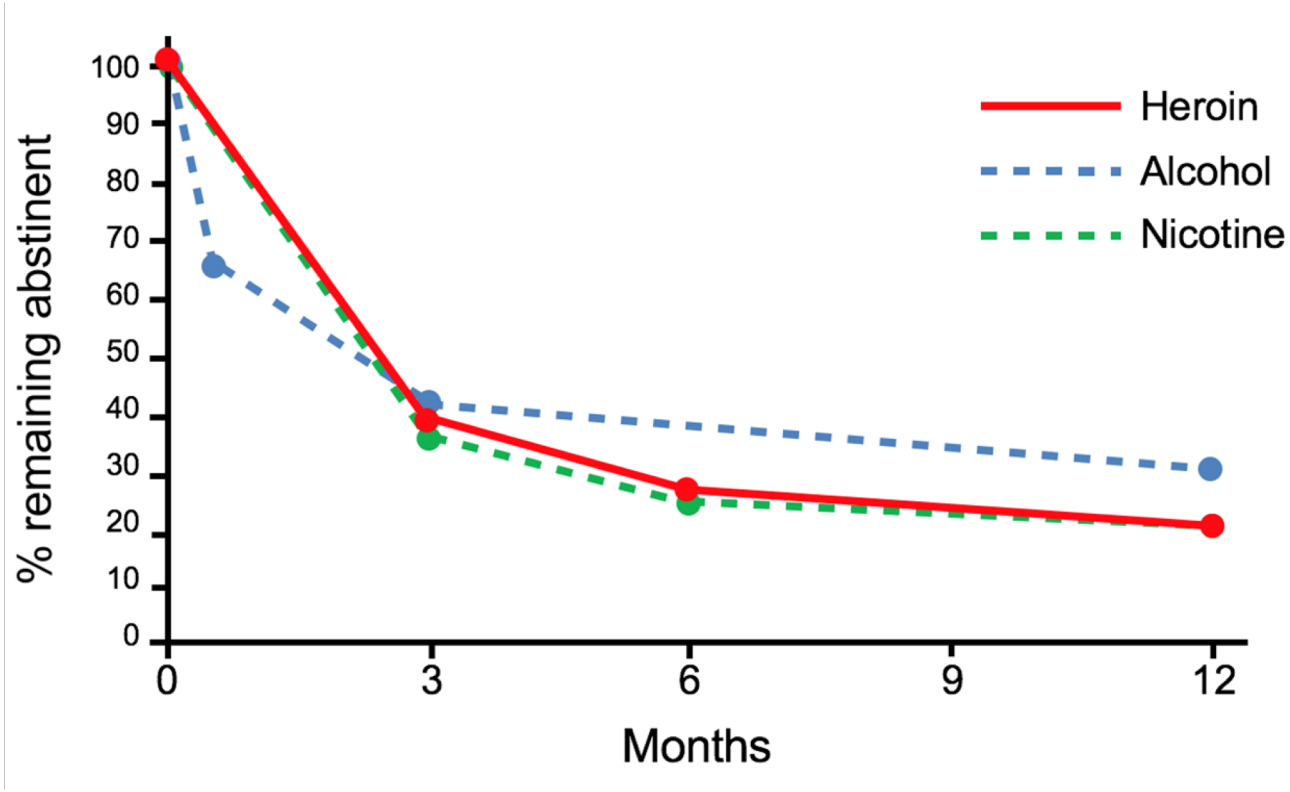
- rapid heartbeat
- elevated blood pressure
- elevated temperature
- insomnia, yawning
- dilated pupils
- brisk reflexes
- tearing, runny nose
- sweating, "gooseflesh"
- muscle spasms

Symptoms

- abdominal cramps
- nausea
- vomiting
- diarrhea
- muscle/bone aches
- anxiety

Described as "having the worst flu and GI bug at the same time"

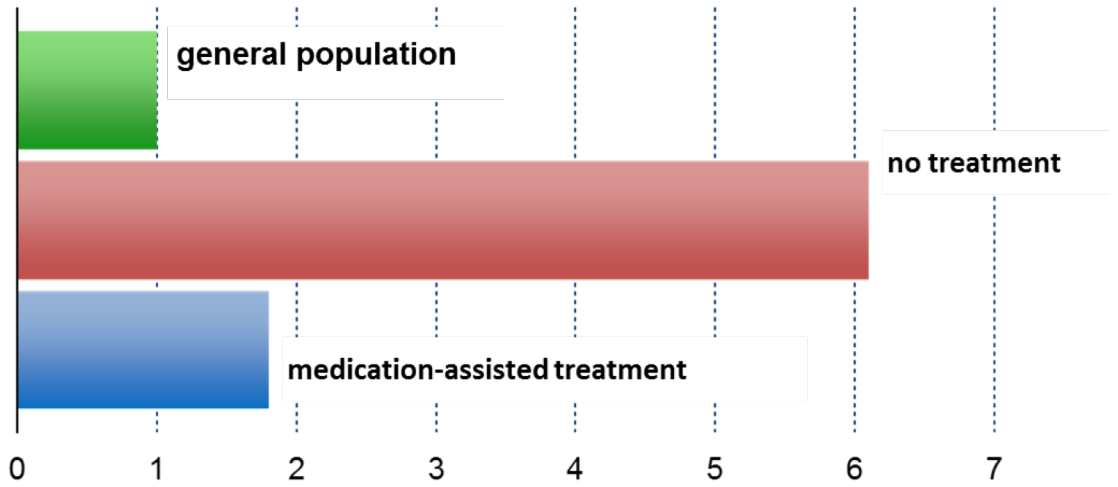
Abstinence without MOUD



Hunt et al 2017

Decreased Mortality with MOUD

Death rates:



Slide from pcssnow waiver training

Dupouy et al., 2017
Evans et al., 2015
Sordo et al., 2017

FDA Approved Medications for OUD

1. **Methadone**
   - Can only be prescribed for OUD in federally certified opioid treatment programs
   - Primarily cash only
   - Covered by Medicaid
2. **Buprenorphine with & without naloxone**
   - Can be prescribed in office-based setting
   - Available in sublingual (under the tongue),long-acting injectable formulations, implant
     - Patch only indicated for pain
   - Covered by insurance
3. **Naltrexone** (not a controlled substance)
   - Office-based setting
   - Tablet or extended-release injection (preferred for OUD)

DHHS: Update on Practice Guidelines for the Administration of Buprenorphine for Treating Opioid Use Disorder 4/28/2021

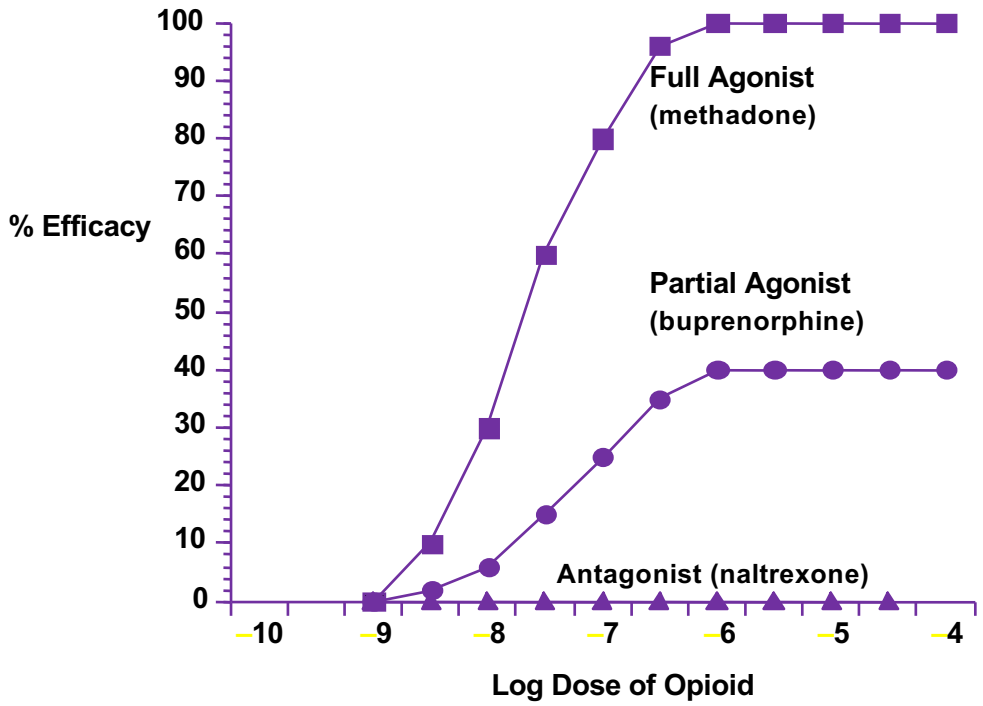
- Eligible physicians, PAs, NPs, Clinical Nurse Specialists, Certified Nurse Anesthetists, and Certified Nurse Midwifes who are state licensed and registered by the DEA to prescribe controlled substances
- May treat up to 30 patients without the waiver training
- Do not have to certify that they have the capacity to provide counseling or ancillary services
- Will be required to submit an application designated as a "Notice of Intent" in order to prescribe buprenorphine for the treatment of OUD

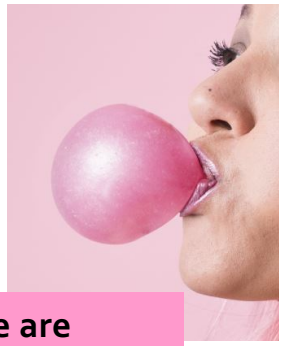
Methadone and other full agonists: fully unlock the door and chain

Buprenorphine (partial agonist): unlocks the door with chain still on and gums up the lock

Naltrexone (antagonist): Jams the lock

More pharmacology





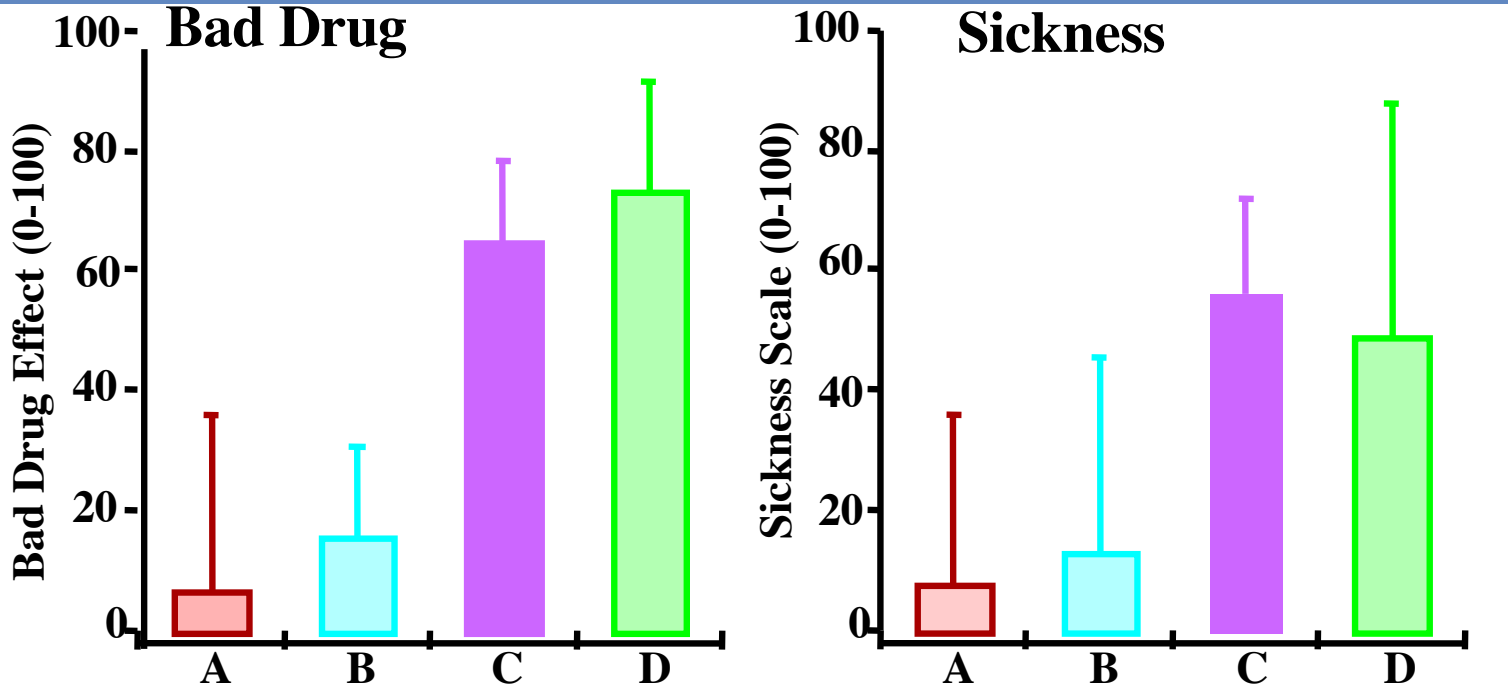
Buprenorphine and naltrexone are "stickier" on the receptor and block activation from opioids

SAMHSA, 2018
Orman & Keating, 2009

PEAK EFFECTS – MEAN (±SD)

Mendelson J., et.al. Biol Psychiatry 1997;41:1095-1101

pcssnow waiver training slide



Clinical Opiate Withdrawal Scale (COWS)

Score	Withdrawal
<5	None
5-12	Mild [Aim for ≥ 8 for Induction]
13-24	Moderate
25-36	Moderately Severe
>36	Severe

Wesson and Ling 2003

Resting Pulse Rate: (record beats per minute)
Measured after patient is sitting or lying for one minute
0 pulse rate 80 or below
1 pulse rate 81-100
2 pulse rate 101-120
4 pulse rate greater than 120

Sweating: *over past ½ hour not accounted for by room temperature or patient activity.*
0 no report of chills or flushing
1 subjective report of chills or flushing
2 flushed or observable moistness on face
3 beads of sweat on brow or face
4 sweat streaming off face

Restlessness *Observation during assessment*
0 able to sit still
1 reports difficulty sitting still, but is able to do so
3 frequent shifting or extraneous movements of legs/arms
5 Unable to sit still for more than a few seconds

Pupil size
0 pupils pinned or normal size for room light
1 pupils possibly larger than normal for room light
2 pupils moderately dilated
5 pupils so dilated that only the rim of the iris is visible

Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored*
0 not present
1 mild diffuse discomfort
2 patient reports severe diffuse aching of joints/ muscles
4 patient is rubbing joints or muscles and is unable to sit still because of discomfort

Runny nose or tearing *Not accounted for by cold symptoms or allergies*
0 not present
1 nasal stuffiness or unusually moist eyes
2 nose running or tearing
4 nose constantly running or tears streaming down cheeks

GI Upset: *over last ½ hour*
0 no GI symptoms
1 stomach cramps
2 nausea or loose stool
3 vomiting or diarrhea
5 Multiple episodes of diarrhea or vomiting

Tremor *observation of outstretched hands*
0 No tremor
1 tremor can be felt, but not observed
2 slight tremor observable
4 gross tremor or muscle twitching

Yawning *Observation during assessment*
0 no yawning
1 yawning once or twice during assessment
2 yawning three or more times during assessment
4 yawning several times/minute

Anxiety or Irritability
0 none
1 patient reports increasing irritability or anxiousness
2 patient obviously irritable anxious
4 patient so irritable or anxious that participation in the assessment is difficult

Gooseflesh skin
0 skin is smooth
3 piloerrection of skin can be felt or hairs standing up on arms
5 prominent piloerrection

Total scores

with observer's initials

Consideration of Medication Choice

	Methadone	Buprenorphine	ER Naltrexone
Mechanism of Action	Full agonist	Partial agonist	Antagonist (non-opioid)
Location	**Federal designated clinic**	**Office based**	Office based
Affinity (stickiness)	Weak	High	High
Half-life	25-60 hours	24-36 hours	5-10 days
Respiratory depression	Respiratory depression and arrest in overdose	**Less respiratory depression (unlikely by itself fatal OD)**	No risk
Precipitated withdrawal	No risk	High	High if opioids on board
Psychosocial treatment	**Built-in**	Waivered need access to	Optional
Who would benefit	**Observed dosing** **Unable to abstain on bup** **Unable to secure bup** **↑ structure & support**	Able to adhere office-based tx Improved safety	**Prefer non-opioid** **Employment restrictions** **Abstinent/risk for relapse** **Hx failed tx with bup/methadone**

Adverse Effects

	methadone	Buprenorphine tabs	ER Naltrexone
Withdrawal	Yes	Yes	No
CNS	Headache, dizziness, drowsiness, insomnia		Headache
cardiovascular	**Rhythm problems**		
Respiratory	Depression		
Gastrointestinal	Abdominal pain, nausea, constipation		Nausea, ↓ appetite
Hepatic			↑ liver enzymes
Neuromuscular	osteoporosis		
Endocrine	↓ testosterone, amenorrhea, weight gain		
Dermatologic	↑ sweating, itching	mouth pain/redness	Injection site pain, swelling
Drug Interactions	CNS depressants, many	CNS depressants	Few, opioids

Comparative Effectiveness of Different Treatment Pathways

Study Parameters

- Total ~ 41,000 individuals
  - 54% male, 74% white
  - 45% comorbid mental health dx (depression & anxiety most common)
- Examined deidentified claims 10/14-12/2017
- OUD diagnosed based on 1 or more inpatient or 2 or more outpatient claims within 3 months (included overdose, injection-related infection, inpatient detox/residential, or MOUD claims

6 mutually exclusive pathways

1. No treatment (~5%)
2. Inpatient detox or residential tx (~16%)
3. Intensive behavioral health (~5%)
4. Buprenorphine or methadone (~13%)*
5. Naltrexone (~2%)
6. Non-intensive behavioral health (~59%)

***Only buprenorphine or methadone was associated with reduced risk of OD and serious opioid-related acute care at the 3- and 12-month follow-up**

Wakeman et al. JAMA Network Open. 2020: 3(2):e1920622

Recovery is harder than it looks from the outside looking in

- We are asking people to exert a heroic level of discipline & sustained determination to develop self-control that is counter to neurobiological drives. All too often primarily supported with incentives based on fear (loss of job, relationships, health etc.)
- In general, do not recommend or encourage people to stop MOUD
- Risk of relapse and inadvertent fatal overdose should be discussed as part of shared decision-making

How long is long enough?

- Overall studies show that ~50% discontinue treatment 3-6 months . Studies up to 16 weeks show high rates of relapse following discontinuation.
  Shulman 2021. BMC
- Continue as long as individual is benefiting from treatment (↓ substance use, ↑ psychosocial functioning)

- Can consider dose reduction.
- Leave door open to increase dose or return or return to treatment if begin
- Consider transition to extended-release naltrexone

Tapering Readiness Inventory

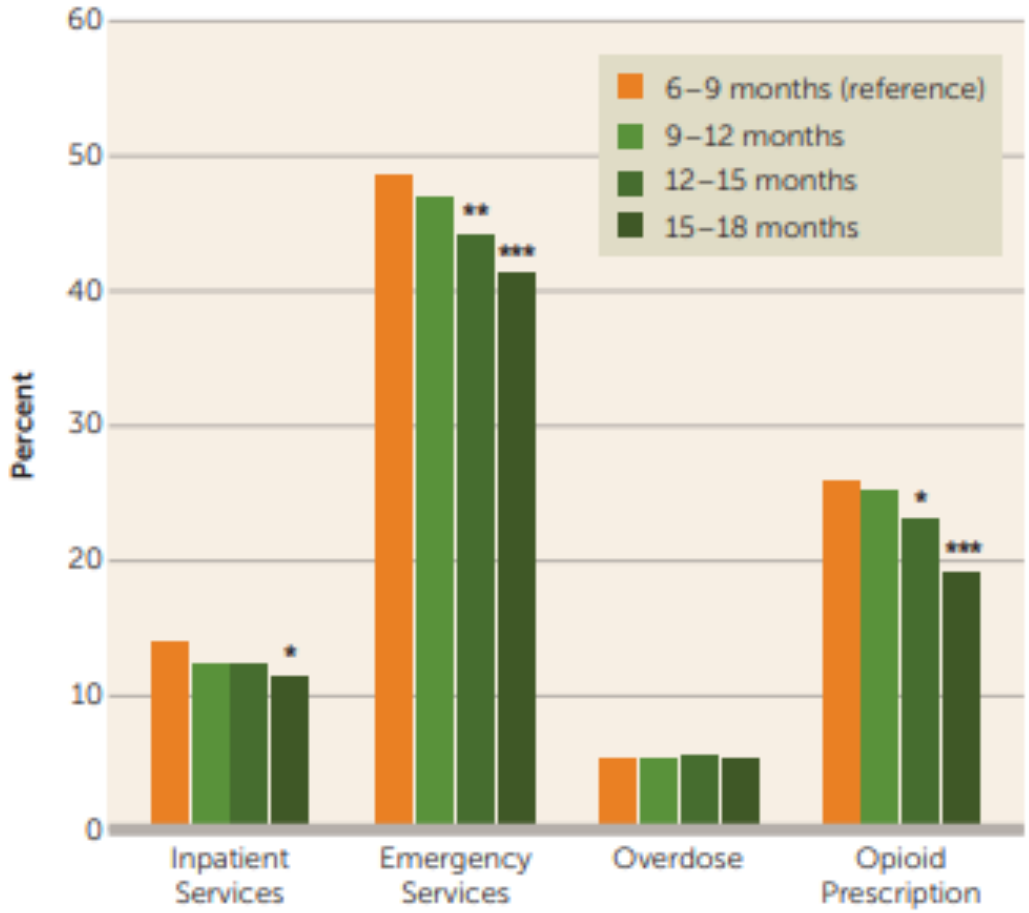
- 16 questions such as
  - Do you think you are able to cope with difficult situations without using drugs?
  - Do you have straight (non-user) friends that you spend time with?
  - Do you think you would ask for help when you are feeling bad during a taper?

https://www.opiatesupportgroup.com/wpcontent/uploads/2015/09/Tapering_Inventory1.pdf

CSAT 1994

5 Year Prospective Effectiveness Trial in England

- 54,347 adults entering treatment in 2008-2009
- Outcome measures were successful tx (abstinence, adherent with MOUD, psychosocial tx, met tx goals and mutually agreement to d/c tx and no return for 6 months
- Who was successful? ~22%
  - Heroin alone better than heroin in combo with cocaine
  - Employed
  - Longer duration of treatment (particularly for more than 2 years)



[a] All comparisons are with the reference group (the 6- to 9-month cohort).
*p<0.05. **p<0.01. ***p<0.001.

6-month outcomes following discontinuation

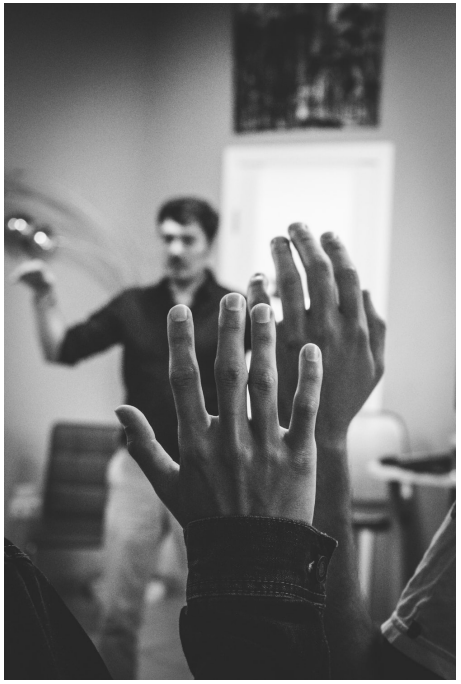
- Review of~27,000 Medicaid beneficiaries, aged 18-64 retained on buprenorphine ≥ 180 days
- Risk of acute care use & OD were high regardless of treatment duration
- Better outcomes in people retained from 15-18 months
- ~5% in all groups had one or more OD

Williams et al. AJP. 2020;177:117-24

Resources

- Funding for medication and treatment available through 301s for uninsured, underinsured who meet certain financial requirements
- Justplainkillers.com for naloxone distribution sites
- Sublocade copay assistance through the INSUPPORT program, Can be as little $5/mo. https://www.sublocade.com/cost-savings?utm_campaign=BR%20%7C%20PAT%20%7C%20Sublocade&utm_source=google&utm_medium=cpc&utm_term=sublocade%20copay%20assistance&gclsrc=aw.ds&&gclid=EAIaIQobChMIy-qoxqT38AIViuGzChoGpgkyEAAYASABEgISPvD_BwE&gclsrc=aw.ds
- Vivitrol Co-Pay Savings Program covers up to $500/mo of copay deductible https://www.vivitrol.com/co-pay-savings-program
- Medication-Assisted Recovery Anonymous (MARA) https://www.mara-international.org/ Zoom meetings available every day

Questions and comments?



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Unique Challenges of Peers		
Date	**Topic**	**Presenter**
6/22/21	Part II: Medications for Opioid Use Disorder	Karen Hartwell, MD

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