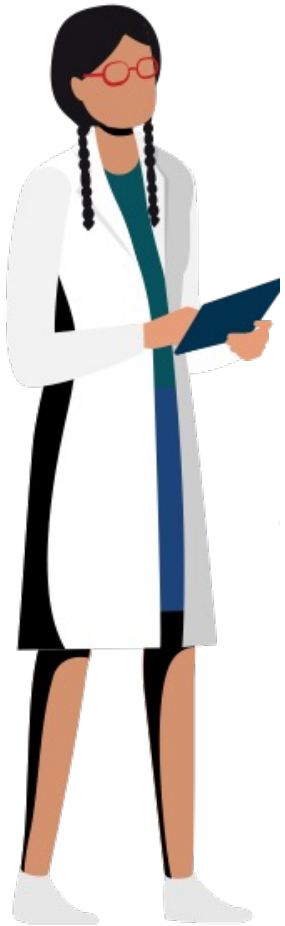




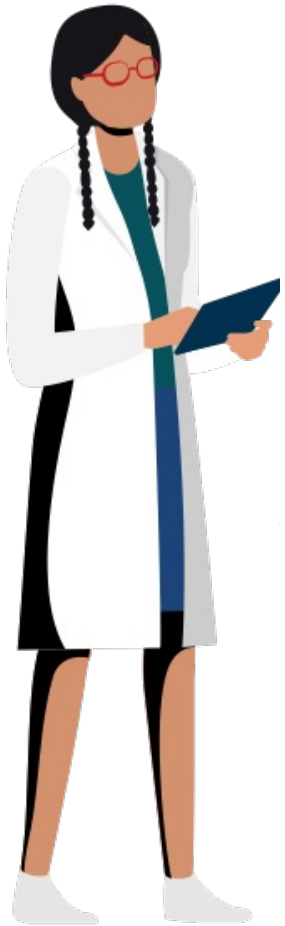
Providing SUD Services

Objectives



1. Review the diagnostic criteria for substance use disorders
2. Overview of the neurobiology of addiction
3. Review office-based medications to treat opioid use disorder

Objectives



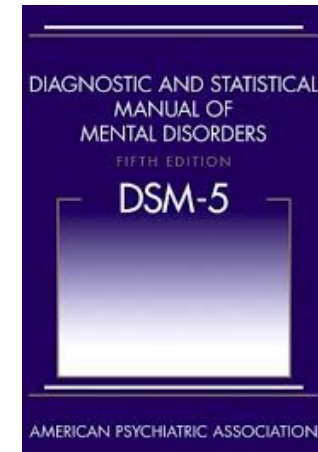
- 1. Review the diagnostic criteria for substance use disorders**

DSM 5

Diagnostic and Statistical Manual
of Mental Disorders

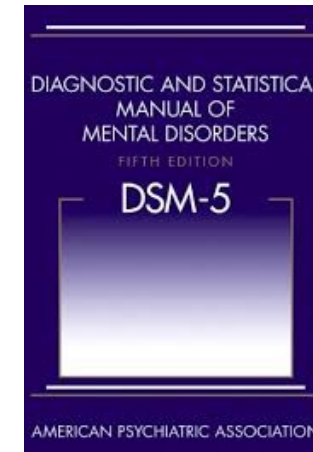
11 criteria

Craving/Compulsion/Consequences/Loss of
Control



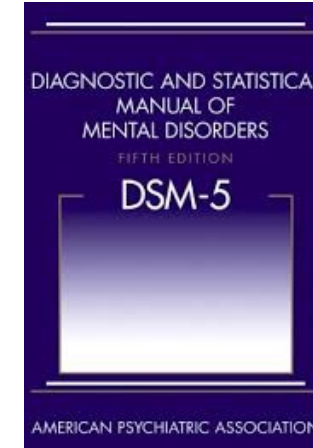
DSM 5: Substance Use Disorder

- Taking in larger amounts or for longer than intended
- Unsuccessful efforts to cut down
- Spending a lot of time obtaining the substance
- Craving or a strong desire to use the substance



DSM 5: Substance Use Disorder

- Continued use despite recurring social or interpersonal problems due to use
- Important activities given up or reduced
- Recurrent use in physically hazardous situations
- Persistent / Recurrent physical or psychological difficulties from use
- Recurrent use resulting in a failure to fulfill major role obligations



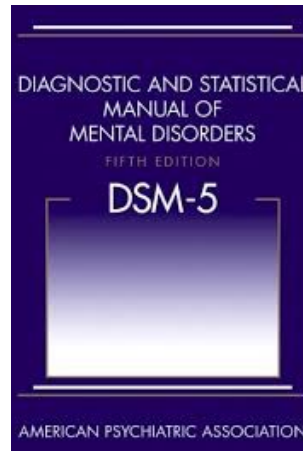
DSM 5: Substance Use Disorder



Tolerance*



Withdrawal*



Substance Use Disorder

2–3

mild disorder

4–5

moderate disorder

6+

severe disorder

Substance Use Disorder



Substance Use Disorder

Diagnosis



Addict

Label/Accusation

The words we use to describe our patients affects the care they receive

Substance Use Disorder

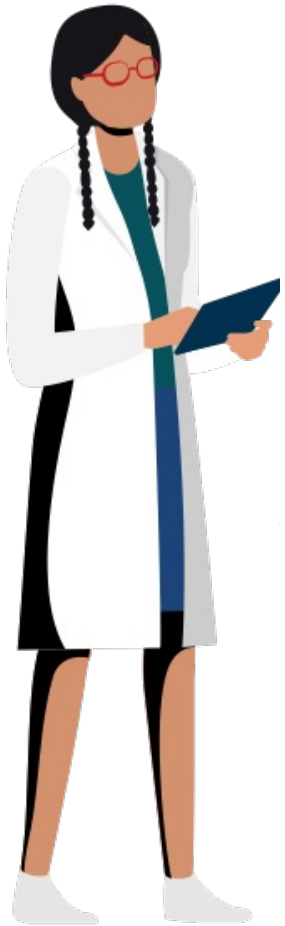
Recovery Dialects
The words we use matter.

Positive	Negative
Person who uses substances	Substance Abuser
Recurrence of Use	Relapse
Pharmacotherapy	Medication-Assisted Treatment
Accidental Drug Poisoning	Overdose
Person with a Substance Use Disorder	Addict
	Alcoholic
	Opioid Addict

While some negative language is okay to use in mutual aid meetings, its use should be avoided in public, when advocating and in journalism.

SOURCE: Ashford, R. D., Brown, A. M., & Curtis, B. (2018). Substance use, recovery, and linguistics: The impact of word choice on explicit and implicit bias. *Drug and Alcohol Dependence*, 189, 131–138.

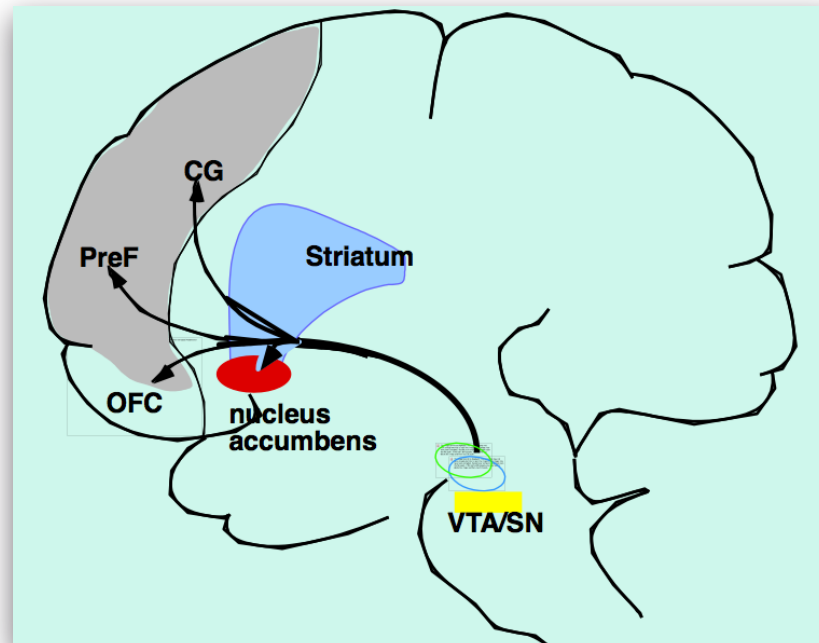
Objectives



2. Overview of the neurobiology of addiction

Overview of the neurobiology of addiction

Mesolimbic Dopamine System

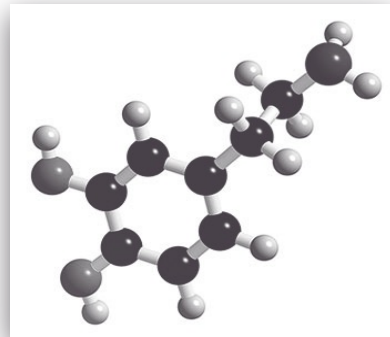


Overview of the neurobiology of addiction

1950s : electrodes



1970s: Dopamine



Desire and Drives

Overview of the neurobiology of addiction

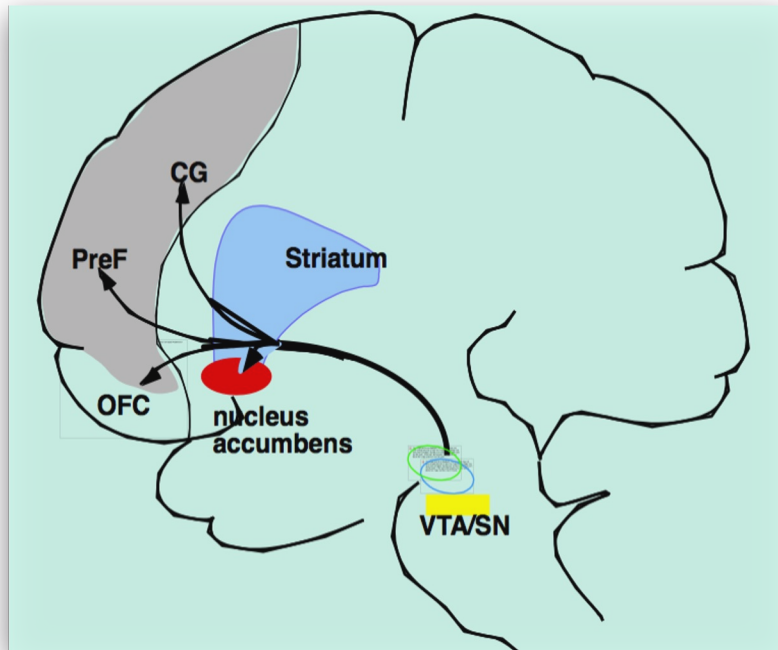


The use of dopamine neurons to shape responses to rewards is seen in simple organisms like worms and flies.

It evolved millions of years ago.

Dopaminergic impulses tell organisms to move toward reward (warmth, food, moisture)

Overview of the neurobiology of addiction



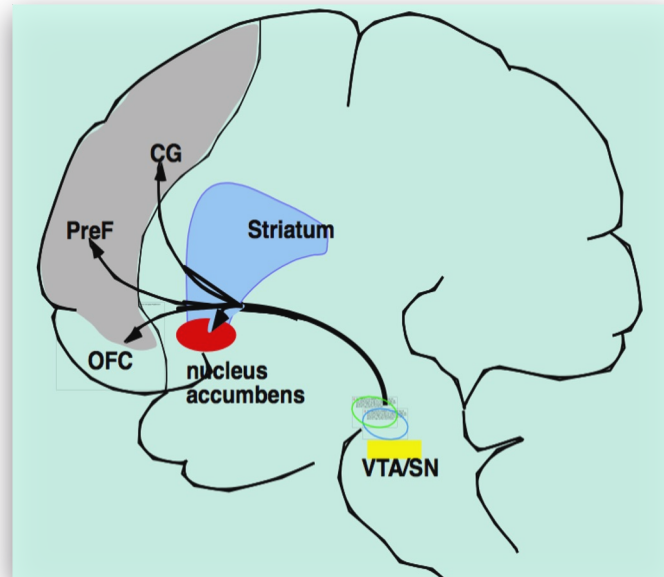
- In humans, those dopaminergic impulses travel through the NAC
- Mediates responses to food, sex, social interactions
- DA projections from VTA to NA release DA and tell the NA to go for it!
- Connects with memory and emotional centers so it can be repeated in the future

Overview of the neurobiology of addiction



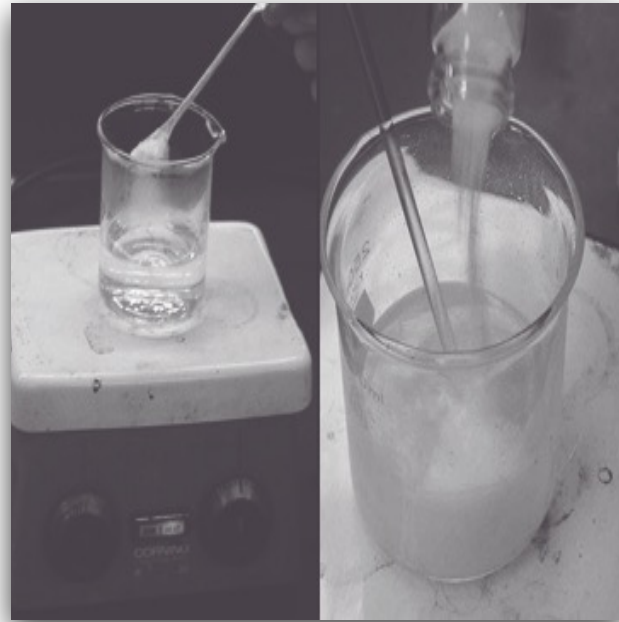
1. Hungry cavewoman eats berry. It is sweet and pleasurable
2. Brain pays very close attention to what she had to do to get that berry
3. Sees the berry bush again, more likely to remember the berry, even craves the berry. Eats the berry.
4. Lives

Overview of the neurobiology of addiction



- Addiction taps into this normal brain process
- All addictive drugs activate this pathway
- Drug experience is deeply linked to memory and emotion

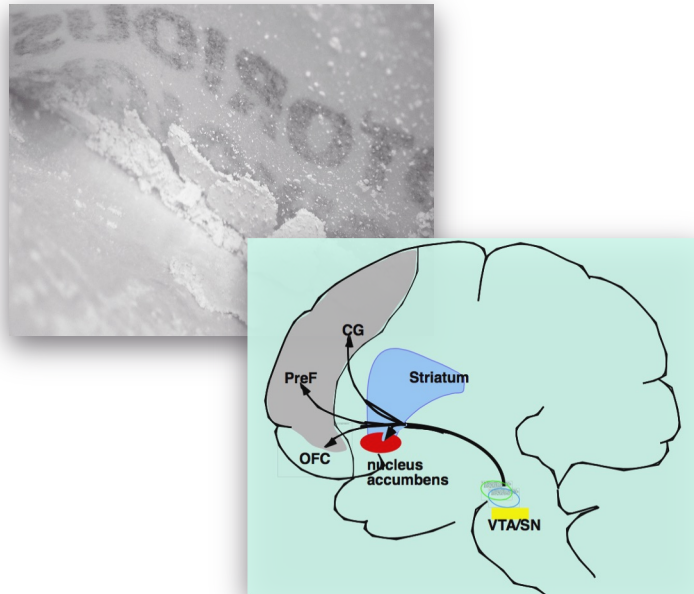
Overview of the neurobiology of addiction



- People, places, things associated with drug use can trigger cravings
- Even when images associated with drug use are shown too rapidly to be “seen” they still trigger cravings

Overview of the neurobiology of addiction

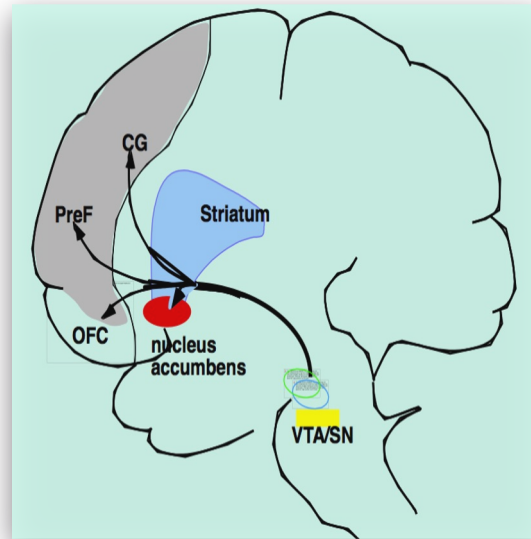
So, part of addiction is craving. Another part is liking



- Opioids: activate DA receptors
- Also activate opioid receptors in NA and produce feeling of satiety, soothing, comfort.

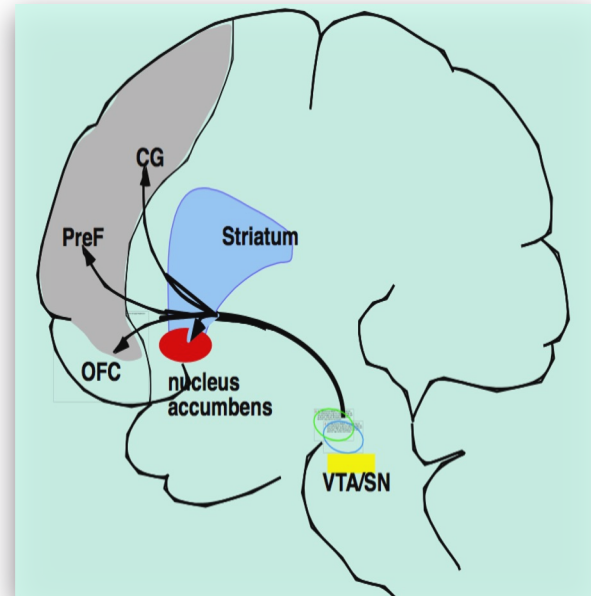
Overview of the neurobiology of addiction

Dysregulation



- Dysregulation: impaired ability of the front of the brain to regulate what is going on in the older regions of the brain.
- Prefrontal cortex helps determine the risks and benefits of behaviors and make rational choices.

Overview of the neurobiology of addiction



- Prefrontal cortex is newer and more complicated. It needs a little time to weigh in.
- Repeated activation of the VTA to NAC track slowly strengthens those connections. Habits get hard wired, fast and automatic

Overview of the neurobiology of addiction



1. Hungry cavewoman eats berry. It is sweet and pleasurable, and she doesn't starve.
2. The berry gives her a headache the next day so she can't hunt well.
3. She has to weigh the benefits and drawbacks of the berries each time she thinks about eating them.
4. If her berry eating habit has become "hard-wired", she may eat them even on days when it is a really, really bad idea

Overview of the neurobiology of addiction

Another complicating factor:



D1: Activate the nucleus accumbens, cause us to act & are responsive to big pleasure surges.



D2: Slow down decision making, allow the frontal cortex to step in. Responsive to smaller pleasures.

Overview of the neurobiology of addiction



Big dopamine surges activate the D1 receptors and cause the D2 receptors to be reabsorbed.

Repeated drug use speeds up the Go! in the nucleus accumbens and inhibits the stop.

Like stepping on brakes of car barreling down a hill only to discover that brakes have been disconnected.

Overview of the neurobiology of addiction



Little pleasures like family, friends, jobs well done, tasks accomplished, provide just enough dopamine to activate the D2 receptors and strengthen the impulses that slow things down.

Medications to decrease craving, attenuate withdrawal symptoms, and decrease deaths

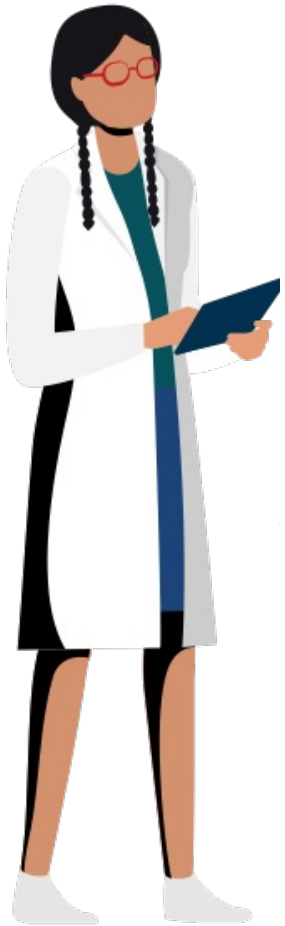
Behavioral interventions that entrain different habits

Overview of the neurobiology of addiction

Conclusion

- Addiction taps into normal brain processes
- It is entrained through habit
- It can be effectively treated

Objectives

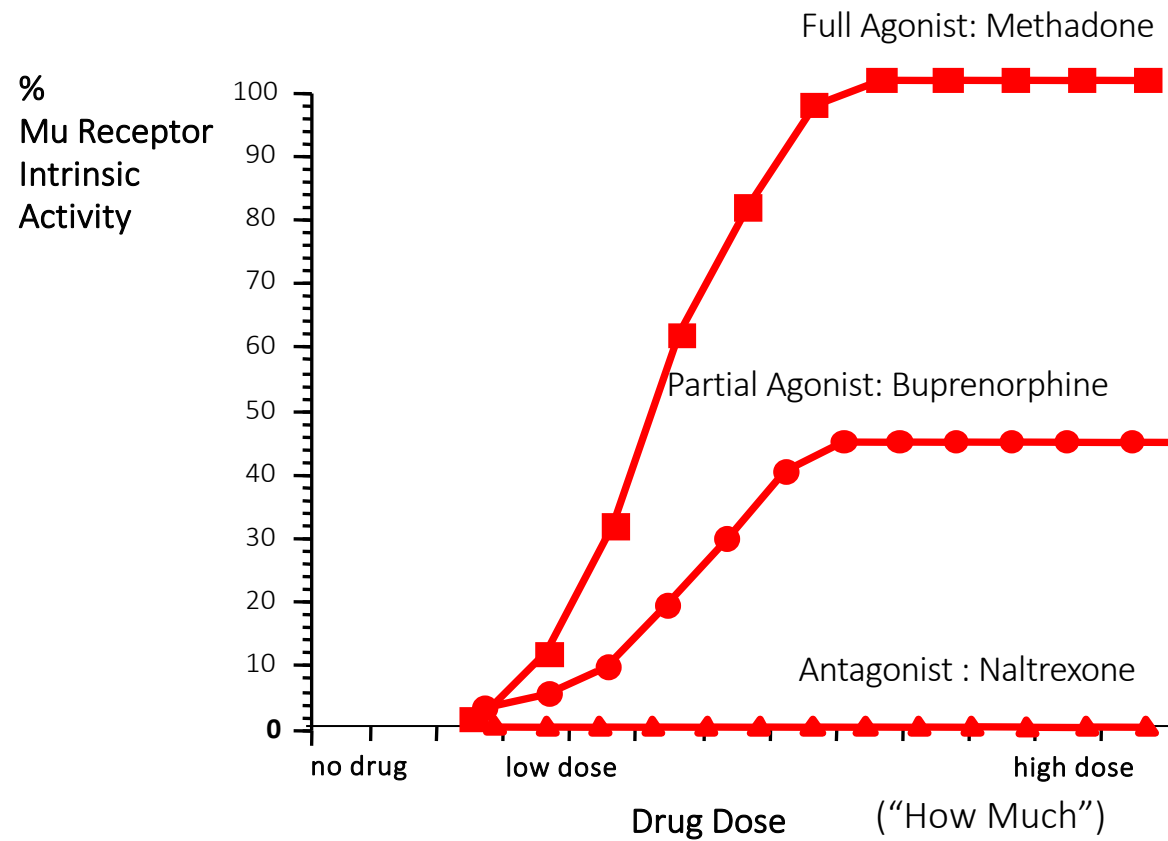


3. Review office-based medications to treat opioid use disorder

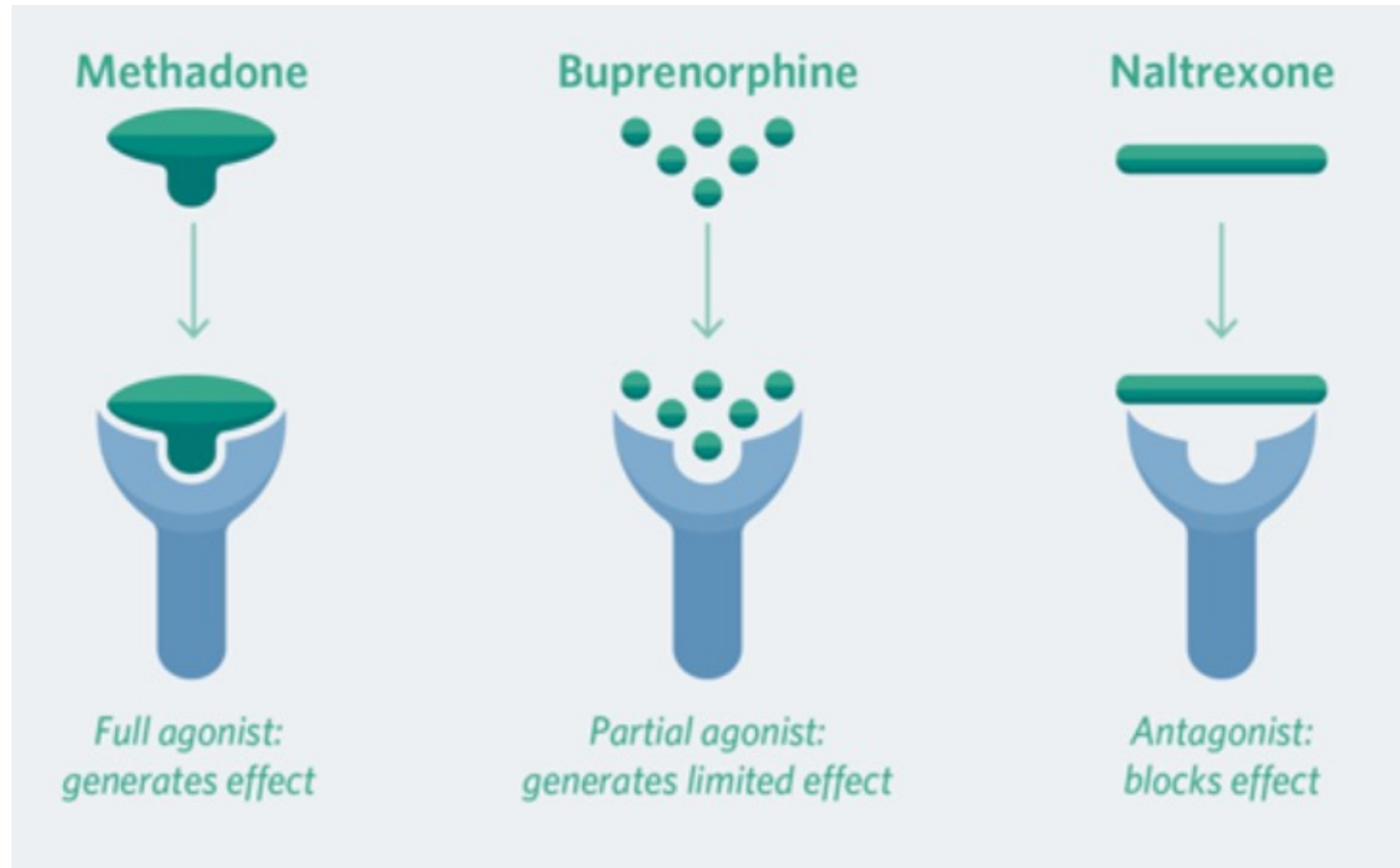
What are they?

Methadone
Buprenorphine
XR- Naltrexone

Pharmacotherapy for Opioid Use Disorder



Pharmacotherapy for Opioid Use Disorder



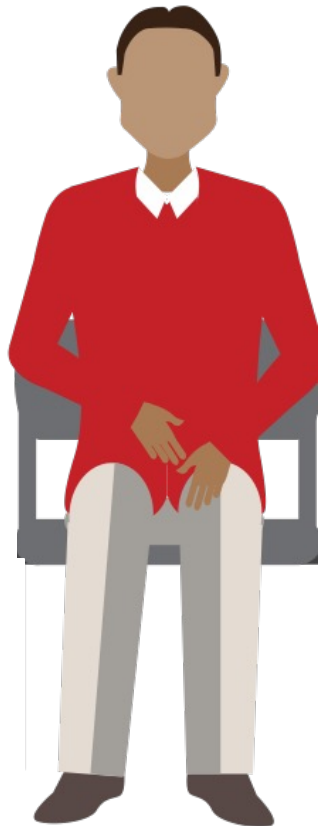
Why do they matter now more than ever?



Fentanyl

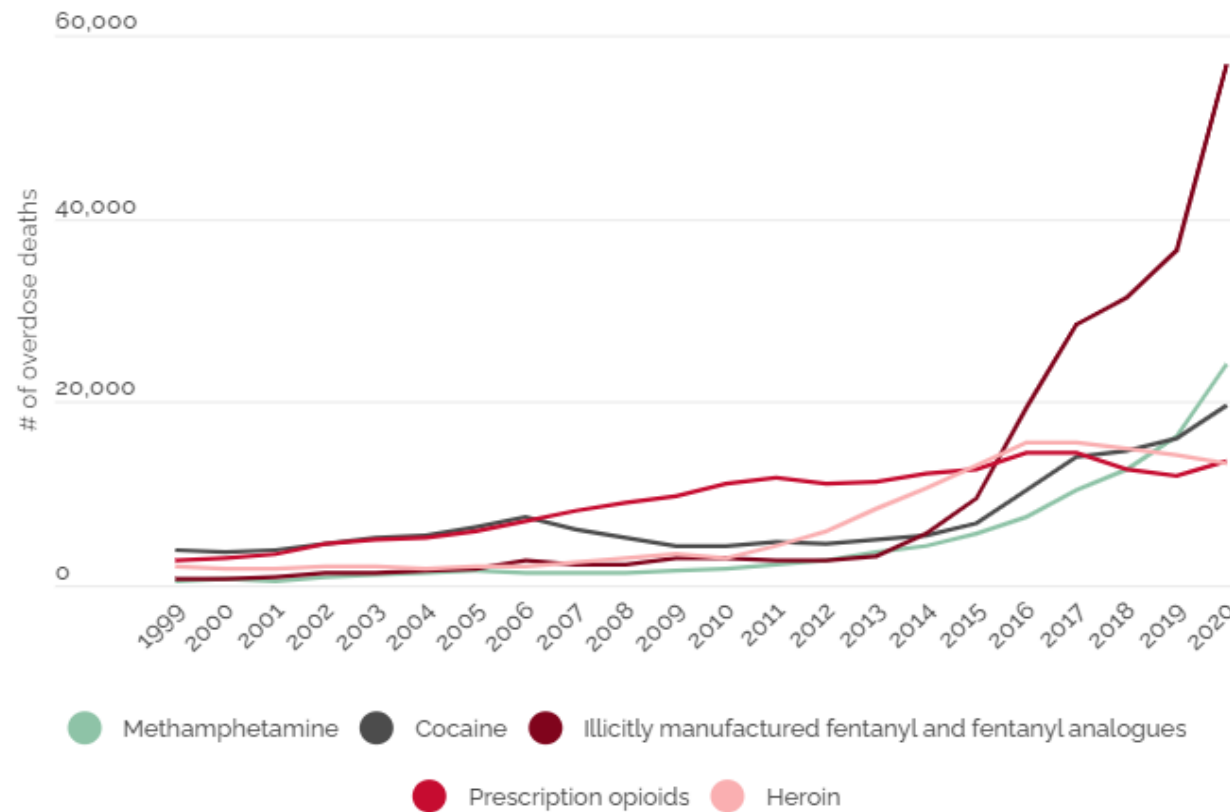


Fentanyl



All Overdose Deaths 1999-2020

Overdose Deaths by Drug 1999-20



(source)

** 2020 numbers are reported provisional deaths per CDC, subject to change

Fentanyl



High affinity and high efficacy at mu receptor

Single use has a short half-life (fast on, fast off)

Repeated use may lead to accumulation in adipose tissue, decreased renal clearance, more mu opioid receptor desensitization

Buprenorphine



Why is it so great?

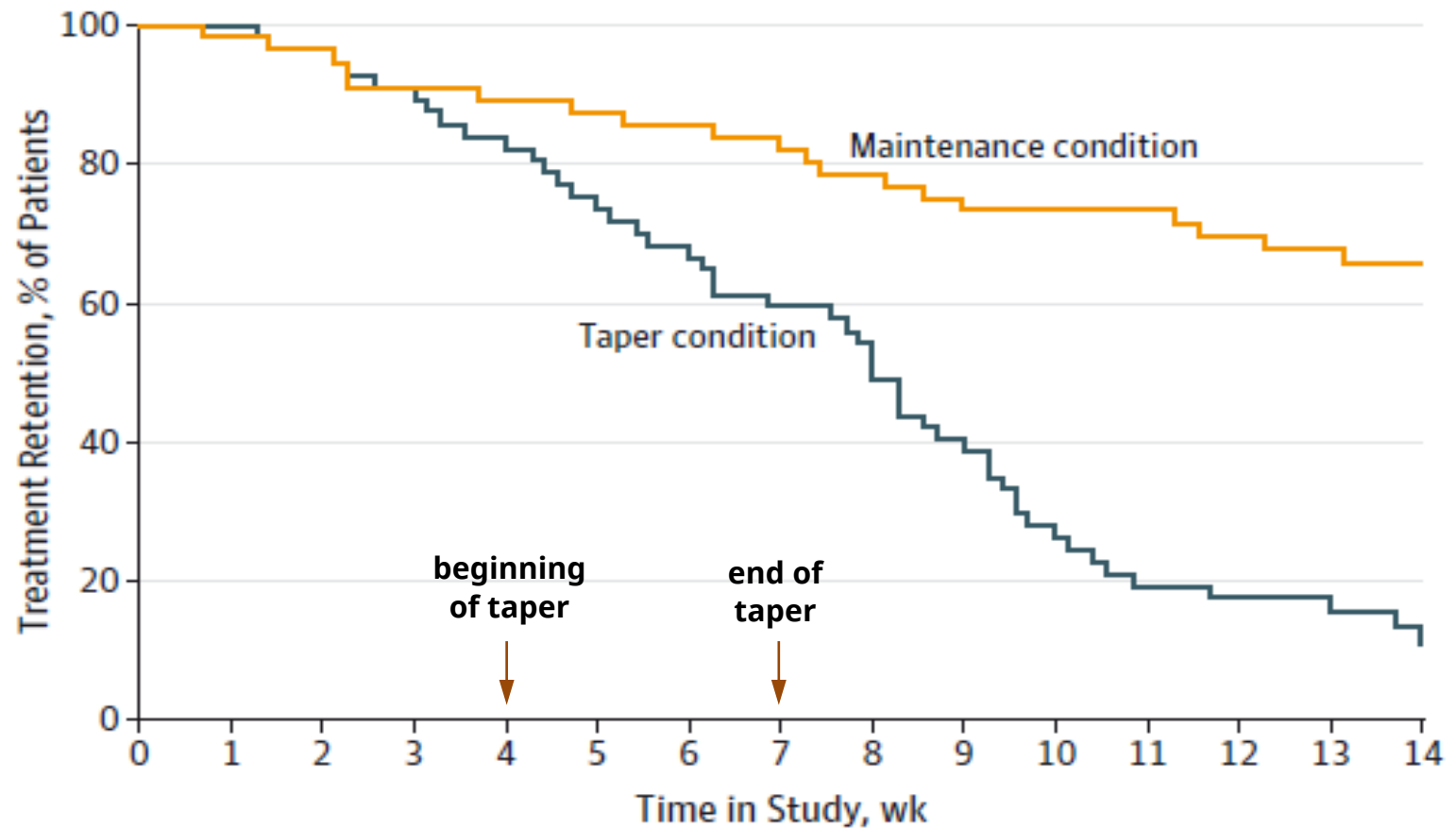
It decreases opioid
cravings, withdrawal, and
use.



Patients taking buprenorphine are significantly more likely to engage and remain in treatment compared to those tapered off the medication.

Fiellen 2014; D'Onofrio 2017

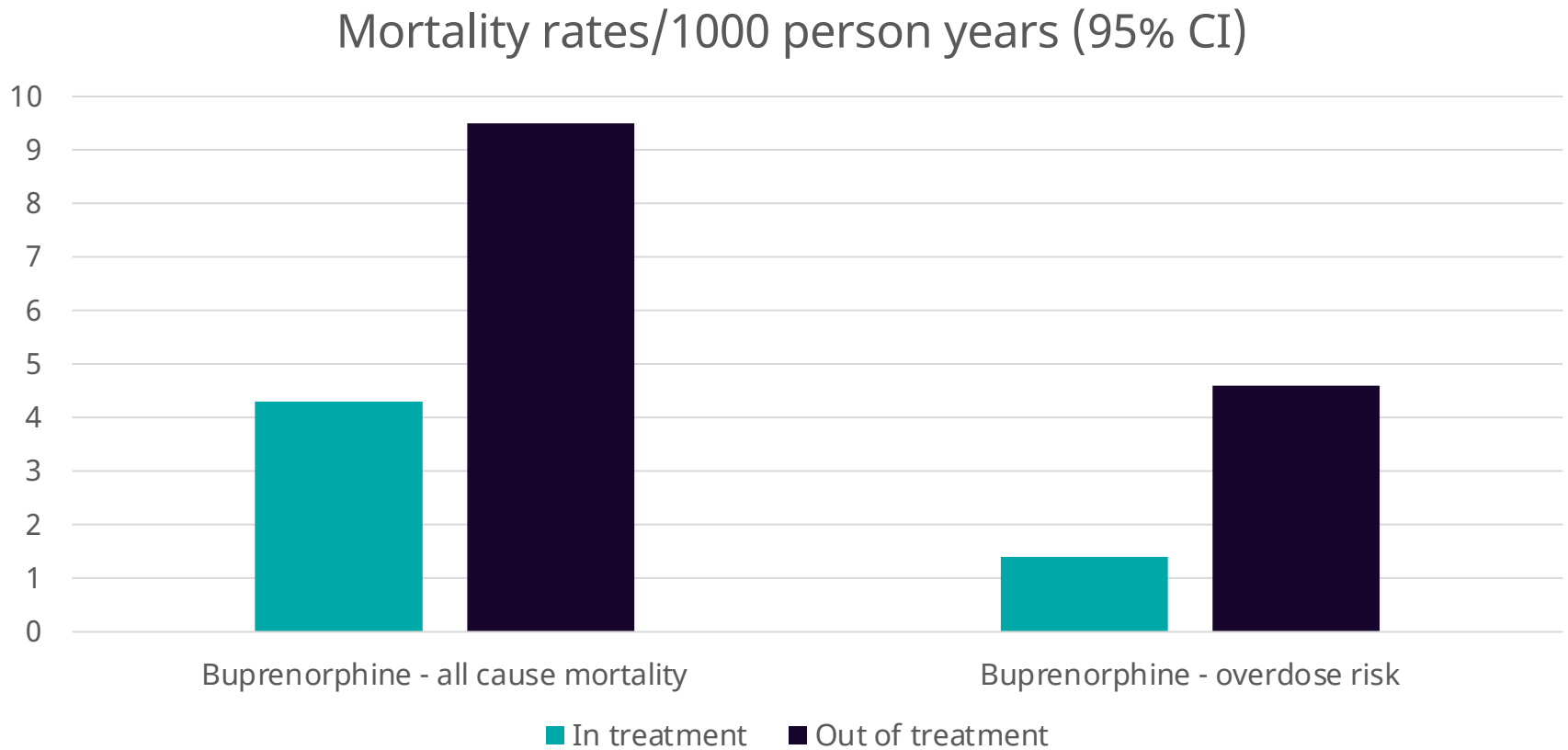
Buprenorphine: Maintenance vs. Taper



Why is it so great?

Most importantly,
people don't die

Mortality Risk during and after buprenorphine treatment



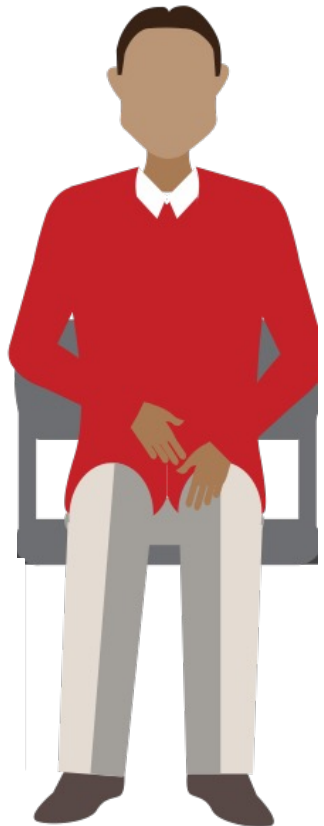
Mortality Risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. Sordo, et al. BMJ 2017.

Important to know:



- Buprenorphine is a high affinity binder at the mu opioid receptors. That means it sits tightly on the receptor.
- It will kick off anything else that's bound there
- But it is a partial agonist at the receptor. That means it doesn't activate the receptor completely.
- If it kicks a full agonist off the receptor, the difference between full agonism and partial agonism is big enough \square precipitated withdrawal

Available in two primary forms:

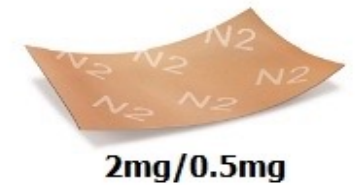


1. Buprenorphine monoprodut (Subutex)
2. Buprenorphine/Naloxone (Suboxone)

Buprenorphine/naloxone may reduce misuse



- Buprenorphine is taken sublingually
- Naloxone is absorbed in minute amounts sublingually.
- It is essentially inactive (in most people) unless injected
- Decreased risk of misuse (controversial)



2mg/0.5mg



8mg/2mg

Newer kids in town: buprenorphine XR (Sublocade and Brixadi)



Sublocade:

Approved November 2017

Single injection lasts one month

Must be refrigerated

Injection hurts

Brixadi:

Approved May 2023

Single injection lasts 1 week or 1 month, various doses

Does not require refrigeration

Injection not as painful



How to administer and prescribe

“Traditional” inductions



- Instruct the patient to abstain from any opioid use for a minimum of:
 - 12-16 hours for short-acting opioids
 - 24 hours for sustained-release opioid medications
 - 36 hours for methadone or fentanyl
- Observe and document mild to moderate withdrawal

“Traditional” inductions



Wait until patient is in mild to moderate withdrawal (which means receptors are empty)

Begin buprenorphine and titrate up, as needed, over 3-4 days



How do you know if a patient is in sufficient enough withdrawal to begin buprenorphine?

Clinical Opiate Withdrawal Scale (COWS)


Clinical Opiate Withdrawal Scale

For each item, circle the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was jogging just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name: _____		Date and Time ____/____/____ : ____:____
Reason for this assessment: _____		
Resting Pulse Rate: _____ beats/minute <i>Measured after patient is sitting or lying for one minute</i> 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120	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	
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	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	
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	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	
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	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	
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	Gooseflesh skin 0 skin is smooth 3 piloerection of skin can be felt or hairs standing up on arms 5 prominent piloerection	
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	Total Score _____ The total score is the sum of all 11 items Initials of person completing Assessment: _____	

Score: 5-12 = mild; 13-24 = moderate; 25-36 = moderately severe; more than 36 = severe withdrawal

Clinical Opiate Withdrawal Scale (COWS)

- 
- Resting pulse rate
 - Sweating/chills
 - Restlessness
 - Pupil size
 - Bone or joint aches
 - Runny nose
 - GI upset
 - Tremor
 - Yawning
 - Anxiety or irritability
 - Goose bumps
- **Guides timing of first dose of buprenorphine**

Traditional induction



Begin buprenorphine with COWS is 10-12

Prepare for Discomfort

- Acetaminophen and ibuprofen
- Clonidine
- Hydroxyzine
- Trazodone
- Tizanidine or Methocarbamol
- Ondansetron
- Bismuth or Loperamide

Srivastara, 2020; Kosten, 2019;
Kuzmaul 2020; Kheirabadi 2008
;Salehi 2011; Sanders 2013

Begin the medication

Give initial dose of buprenorphine (originally 4 mg) and titrate up over a period of hours.



Precipitated Withdrawal



If opioid withdrawal appears shortly after the first dose buprenorphine may have precipitated a withdrawal syndrome

Precipitated Withdrawal



Greatest severity of buprenorphine-related precipitated withdrawal in the first few hours (1-4) after a dose

Challenges with Traditional Induction

- Patient must experience withdrawal, which is difficult
- With fentanyl, sometimes need to wait even longer than 3 days because fentanyl sticks around in the fat
- Always possible that patient will experience precipitated withdrawal



Another option...



ninja clipart PNG Designed By 588ku from
https://pngtree.com/freepng/sneak-attack-sneak-attack-man-in-black-black-man-ninja_3931511.html?sol=downref&id=bef

Low dose buprenorphine induction


- Many different protocols
 - Initial protocol “Bernese Method”
 - Usually start at 0.5 mg
 - Often 7-10 days
 - No universally accepted regimen
 - Can continue full agonists throughout the entire induction

Day	Dose
1	0.5 mg daily
2	0.5 mg bid
3	1 mg bid
4	2 mg bid
5	4 mg bid
6	4 mg tid
7	8 mg tid

Adapted from Yale protocol

⁹Opioid Use Disorder Practice Update (2022)
British Columbia Centre on Substance Use

Rapid low dose inductions



Day	Full Opioid Agonist	Buprenorphine Dosing Instructions	Total Daily Dose of Buprenorphine
1	Continue	0.5 mg SL once	0.5 mg
2	Continue	0.5 mg SL bid	1 mg
3	Continue	1 mg SL bid	2 mg
4	Continue	2 mg SL bid	4 mg
5	STOP (if able to tolerate increase)	4 mg SL once. If tolerated take additional 4 mg in 10 mins. Continue to titrate prn for ongoing cravings or withdrawal symptoms for TDD of 16-24 mg	16-24 mg

Tips and Tricks

- Specifically outline what adjunct meds you are giving and for what
- Instruct patients to take AM buprenorphine before their full agonist



Tips and Tricks

- Close follow up
- Modify or slow protocol as needed (i.e. repeat days)
- Give naloxone to every patient



SL Maintenance

- Continue patient at the dose at which they have no withdrawal symptoms and minimal to no cravings
- The maximum effective dose has long been considered 24mg
- However, with fentanyl, many patients continue to have cravings and withdrawal symptoms at typical doses (16-24 mg)
- It is becoming more common to **up titrate** to 28-32 mg which seems to be helpful for some patients



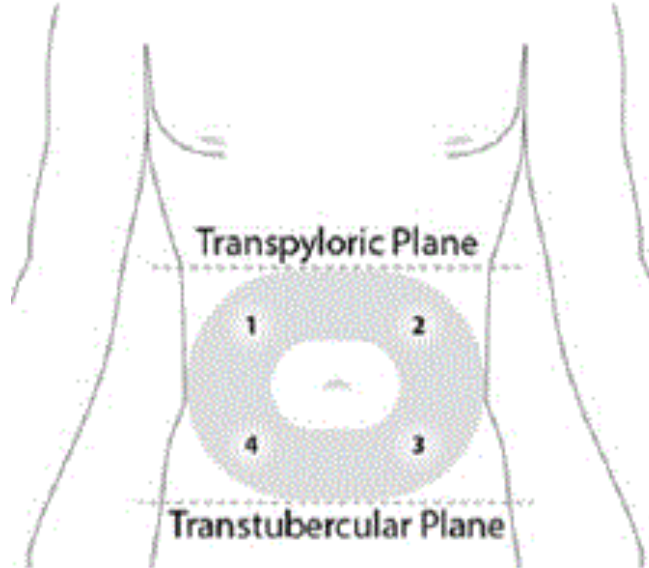
And injectables...

Sublocade & Brixadi

(With gratitude to Trey Draude, PharmD for slide templates and education)



Sublocade Administration

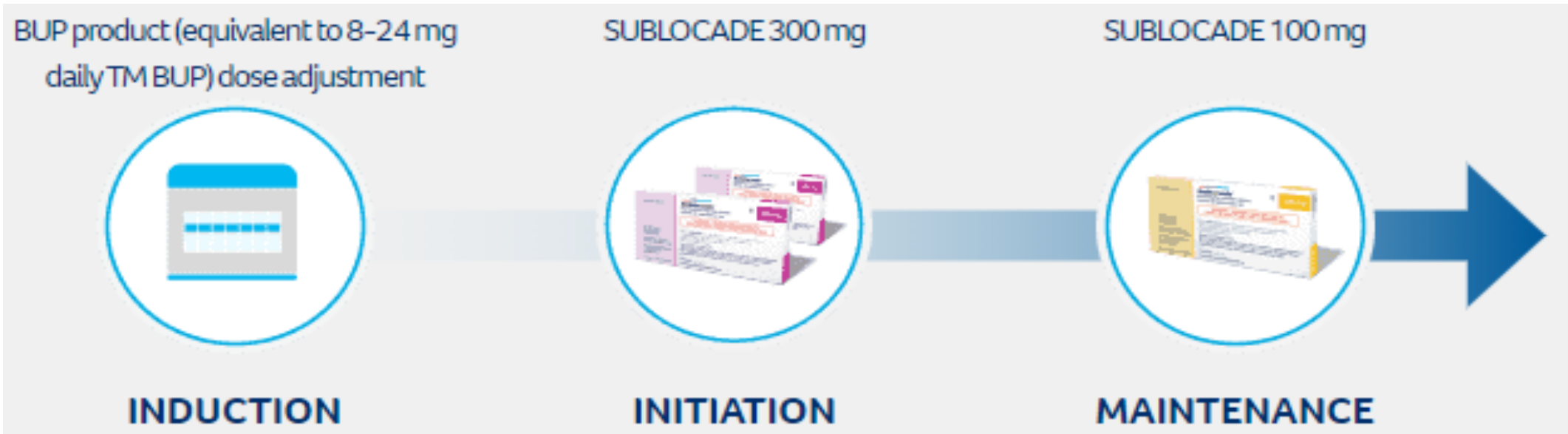


- Sterile Technique
- Subcutaneous
- Abdominal
- By a Trained Health Care Staff
- Remove from fridge prior to injection
- Laying down
- With needle provided in packaging
- Hold and use Gauze to reduce discharge

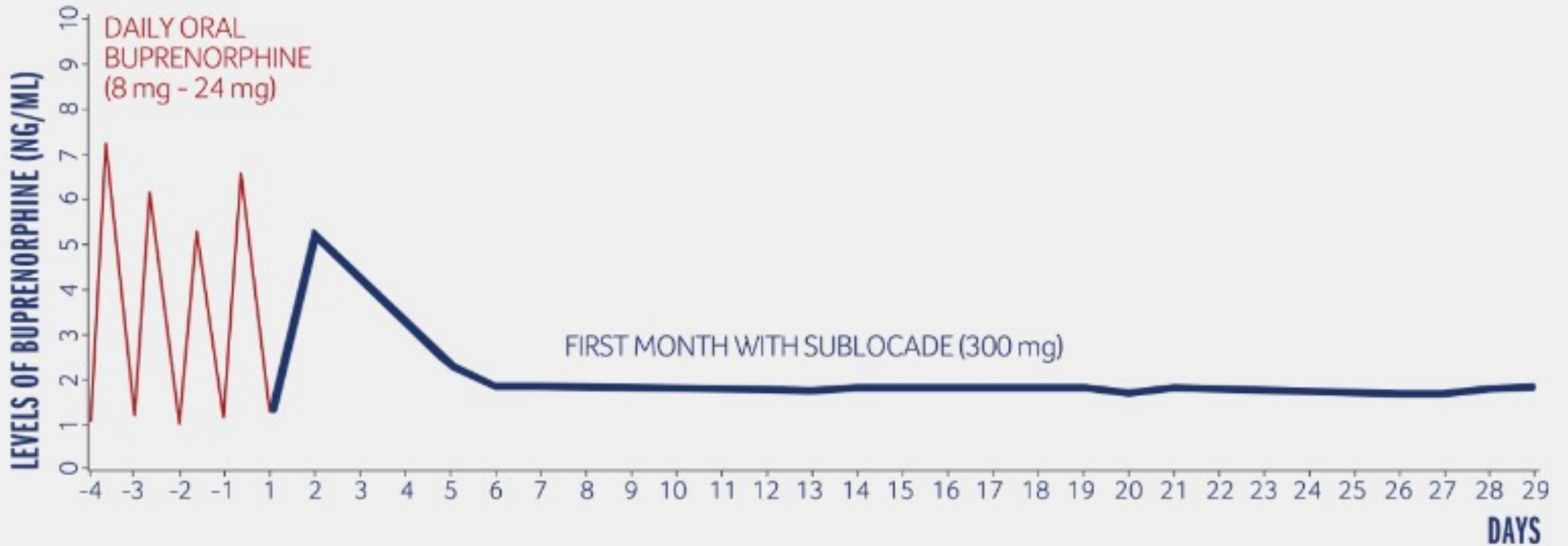
Sublocade Dosing

Doses	Injection #1	Injection #2	Maintenance Dose
8 – 18 mg/day	300 mg	100 mg*	100 mg
20 – 24 mg/day	300 mg	300 mg	100 mg

*For patients still experiencing craving or withdrawal symptoms after the initial 300-mg dose, consider giving 300 mg as the second dose

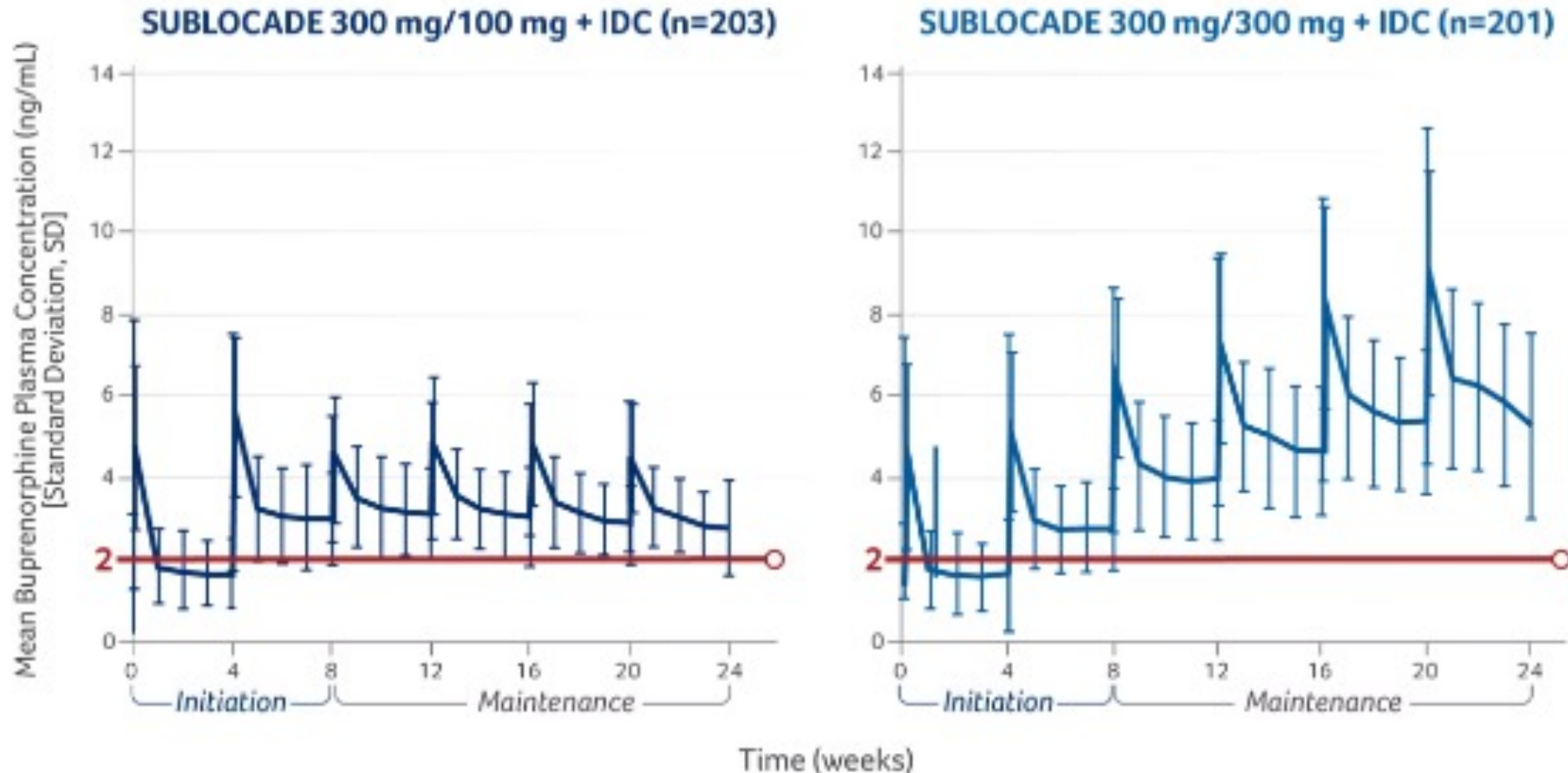


Sublocade Pharmacokinetics



Sublocade Pharmacokinetics

Mean weekly buprenorphine concentration levels³



Brixadi

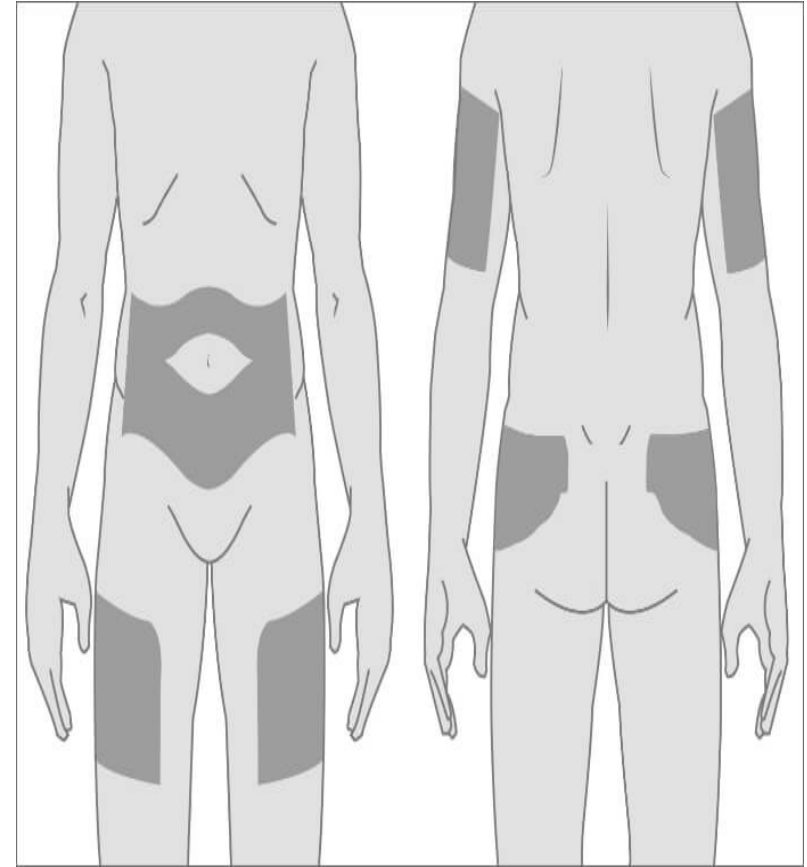
Weekly



Monthly



Brixadi Administration



Dosing & Administration | BRIXADI[®] (buprenorphine) extended-release injection for subcutaneous use (CIII) (brixadihcp.com)

Brixadi Dosing



BRIXADI Weekly should be administered in 7-day intervals



BRIXADI Monthly should be administered in 28-day intervals

Brixadi Dosing




The weekly dose may be given up to 2 days before or after the weekly time point. The monthly dose may be given up to 1 week before or after the monthly time point



Doses of BRIXADI Weekly cannot be combined to yield an equivalent BRIXADI Monthly dose

Brixadi Dosing

Daily Sublingual Buprenorphine Dose*	BRIXADI Weekly		BRIXADI Monthly
≤6 mg	8 mg		-
8-10 mg	16 mg		64 mg
12-16 mg	24 mg		96 mg
18-24 mg	32 mg		128 mg

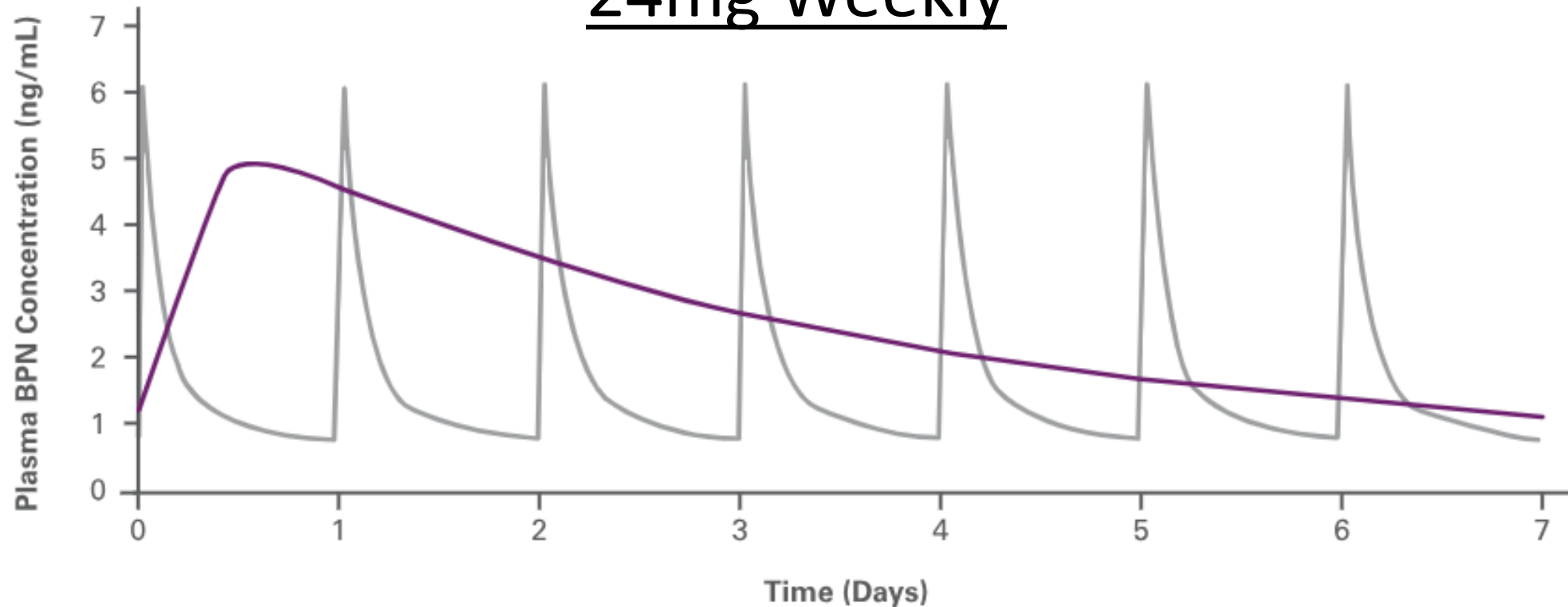
Brixadi Induction Dosing

For those not currently on buprenorphine but who have opioid tolerance:

1. Administer a 4mg “test dose” to rule out precipitated withdrawal
2. If tolerated, administer 16mg Weekly dose followed by 8mg weekly within 3 days
3. Continue with 24mg weekly dosing one week after the 16mg dose was administered and continue with 24mg weekly dosing thereafter.
4. Titrate dose as needed to include transition to monthly dosing

Brixadi Pharmacokinetics

24mg Weekly

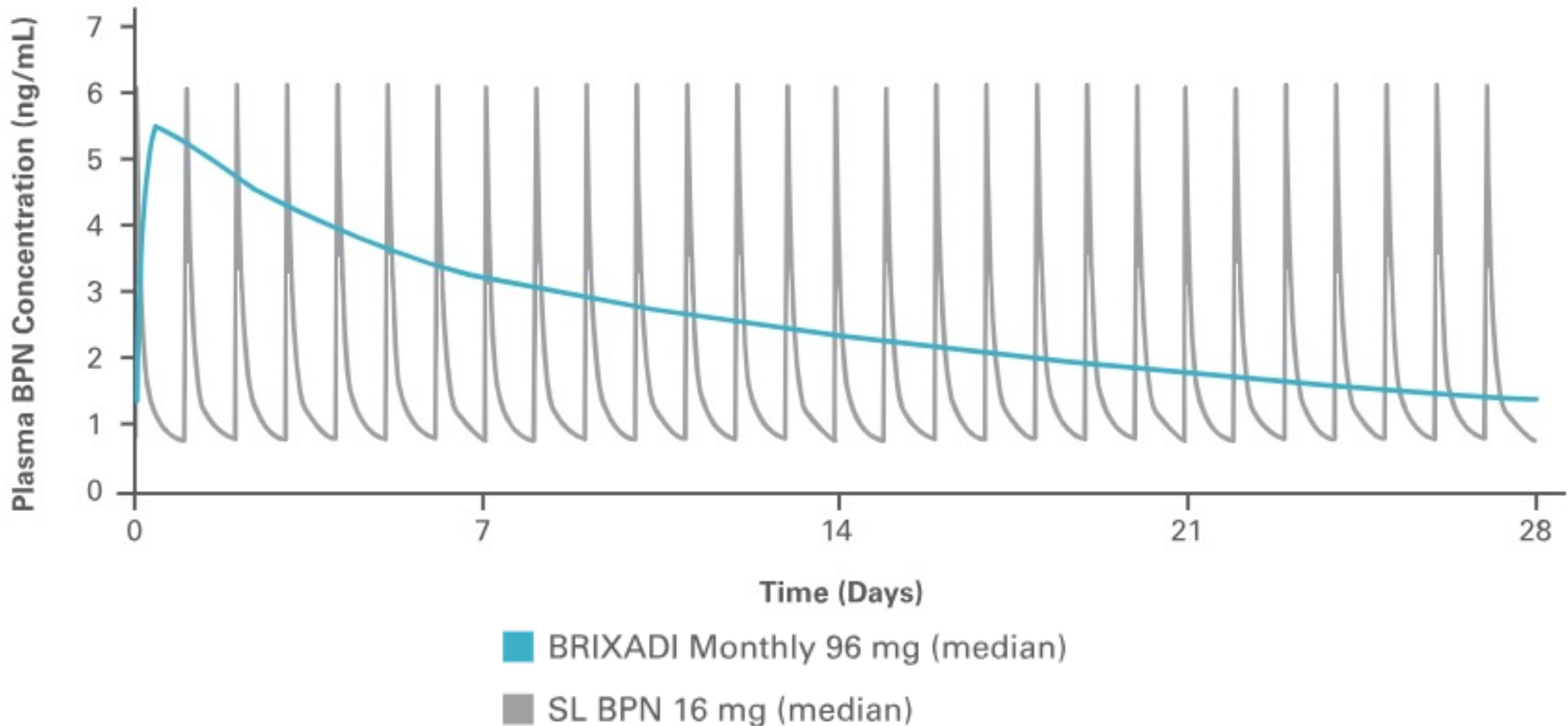


■ BRIXADI Weekly 24 mg (median)

■ SL BPN 16 mg (median)

Brixadi Pharmacokinetics

96mg Monthly



Regulations and Regulatory Changes



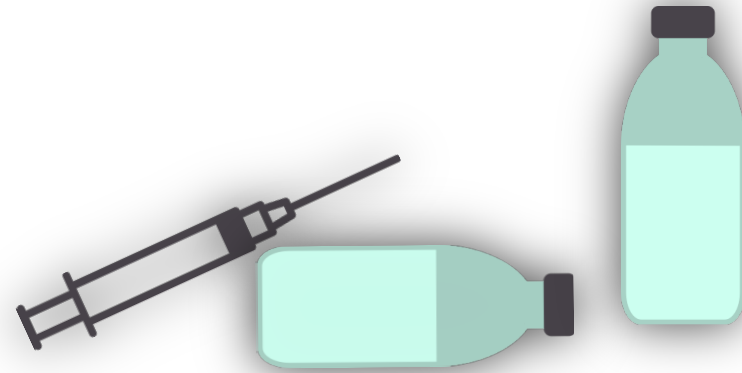
Buprenorphine approved by the FDA in 2002. Prescribers were required to undergo an 8-hour training, register with the DEA, obtain an “X-waiver” and could only prescribe to 30 patients at a time

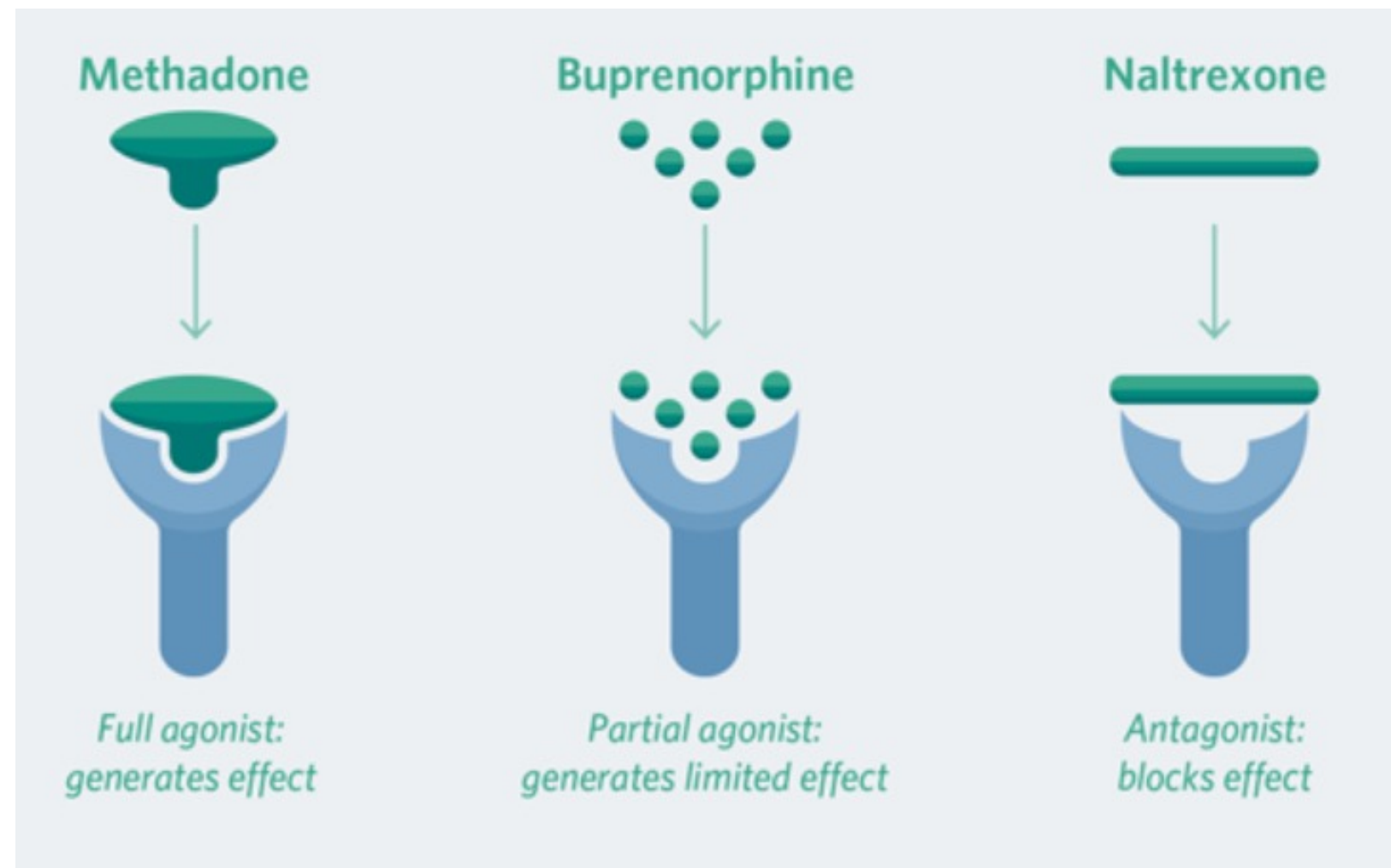
2016 NPs and PAs were allowed to prescribe, but with a longer training requirement. Still required to obtain X waiver and register with the DEA and limit patients

Training requirement removed in 2021, though prescribers still needed to obtain the waiver and register with the DEA

Jan 2023 all buprenorphine specific DEA requirements were removed

Naltrexone for Extended Release Injectable Suspension





Difficult to start

Requires abstinence from opioids 4 – 7 days

About 25% of patients will not complete induction



Overdose data

- Original findings
 - more overdoses in the XR-NTX arm, but not statistically significant
- Re-analysis
 - Researchers had missed cases of overdose
 - 28 overdoses in XR-NTX arm
 - 2.4 x greater hazard of overdose compared to bup/nal

Patient Case

24 year-old man presents to the front desk Thursday at 3 PM

“I don’t have an appointment but I’m using 1 gram of fentanyl powder daily and some ‘clear’ and I need help stopping.”

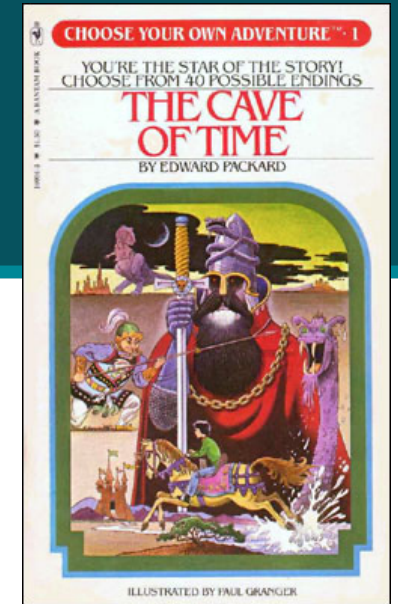
“I OD’ed last week and had to be Narcan’ed and I’m really scared.”



Patient Case

Which of the following are best practices in this clinical scenario?

- A. Arrange for a warm hand-off to behavioral health
- B. Inform the patient that he does not have an appointment and give him a list of local detox centers
- C. Check the provider schedule. You notice that one provider has a no-show and you ask the provider if they would see the patient
- D. A and C
- E. Not sure/Phone a friend



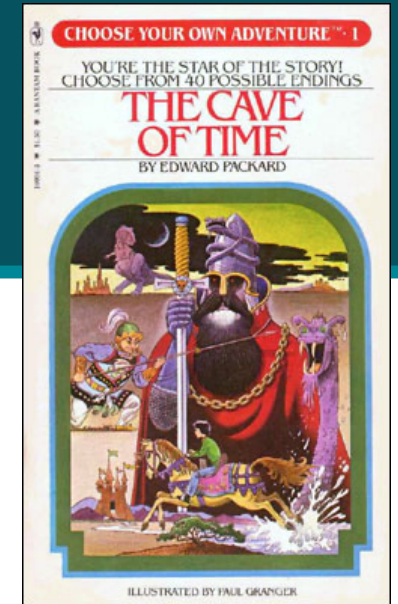
Patient Case

One of the providers has space on their schedule and gets the patient set up in a room.

What other elements of the **history** do you need?

What **diagnosis(es)** do you think this patient has?

What labs and imaging do you **need** before you start treatment?



Patient Case

You determine that Jim (patient) has a **severe opioid use disorder** and probably a **moderate methamphetamine use disorder**. He wants to start buprenorphine and declines a referral to a methadone clinic. He specifically requests 'Subutex' because he does not want any more naloxone in his body.

What are your options for starting buprenorphine?

- A. Wait, I don't have a urine drug screen so I can't start buprenorphine.
- B. I can't start buprenorphine because Jim is also using methamphetamine and cannabis.
- C. Don't I need my x-waiver to prescribe buprenorphine?
- D. I inform Jim that I can only prescribe buprenorphine/naloxone (Suboxone) and I can't start him on buprenorphine mono-product (Subutex).
- E. We discuss different induction options using buprenorphine mono-product.

Patient Case

What options do you give Jim for his buprenorphine induction?

- A. Standard induction
- B. Low dose induction over 7 days
- C. Rapid low dose induction over 3 days
- D. Quick Start Method
- E. Rapid induction onto Sublocade
- F. All of the above
- G. Please, please, no more options.



Summary

- Opioid use disorder can be treated in an outpatient setting
- Buprenorphine saves lives
- Please prescribe

