Non-traditional Buprenorphine Induction

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Today…

- I have nothing to disclose
- I will be discussing off label treatments
- The evidence for burenoprhine induction/ treatment discussed today are based on case reports, case series, as well as institutional experiences

Objectives

By the end of this talk, you will be able to….

- Describe options when buprenorphine induction does not go as planned
- Describe the traditional buprenorphine induction
- Describe basic concept of alternative buprenorphine induction

It will be an interactive session, so I hope you will participate!

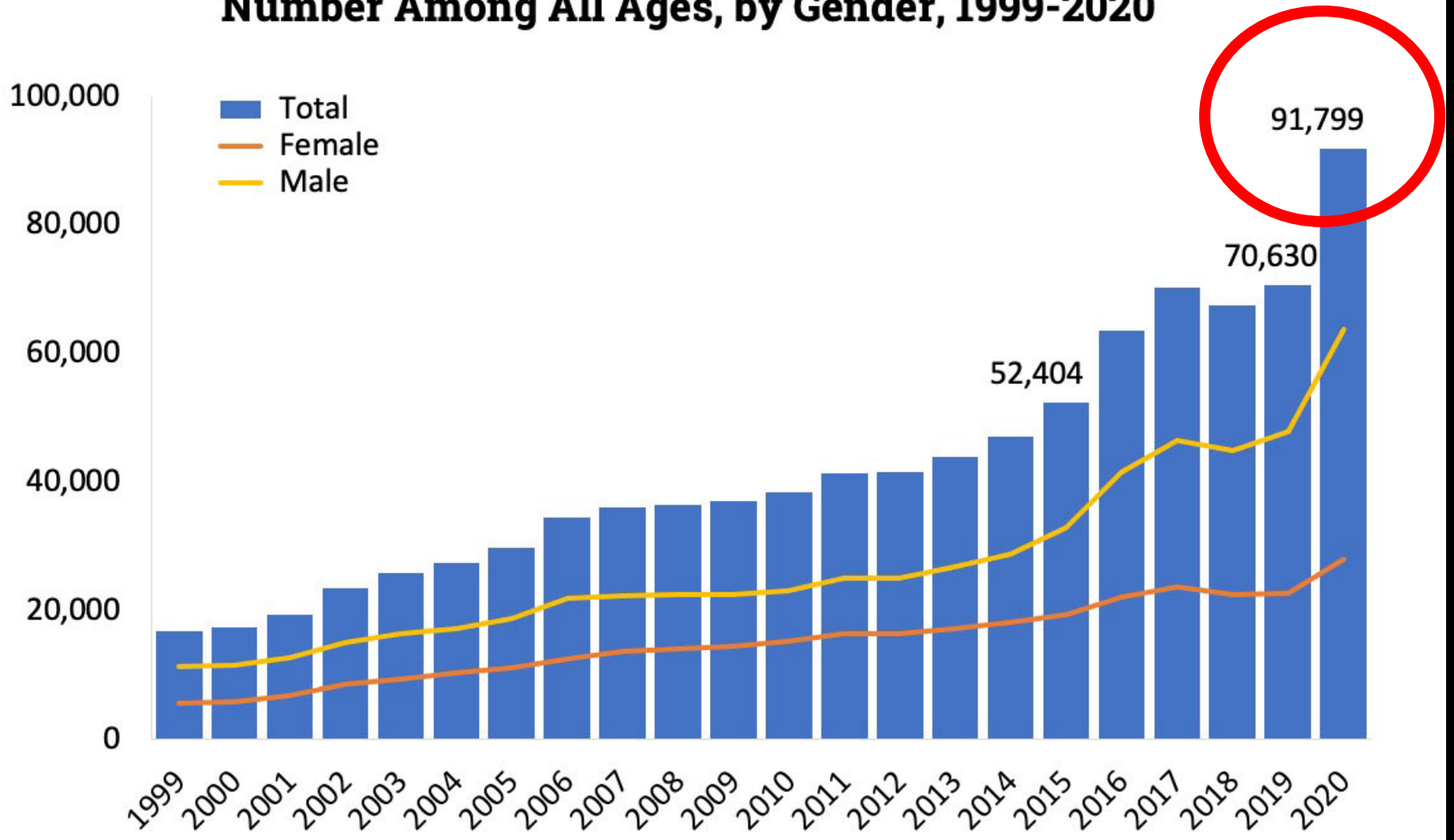
Please hold your questions until the end because I won’t be able to check the chat as I am presenting…!

Why is this topic important?

- https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates

Figure 1. National Drug-Involved Overdose Deaths*

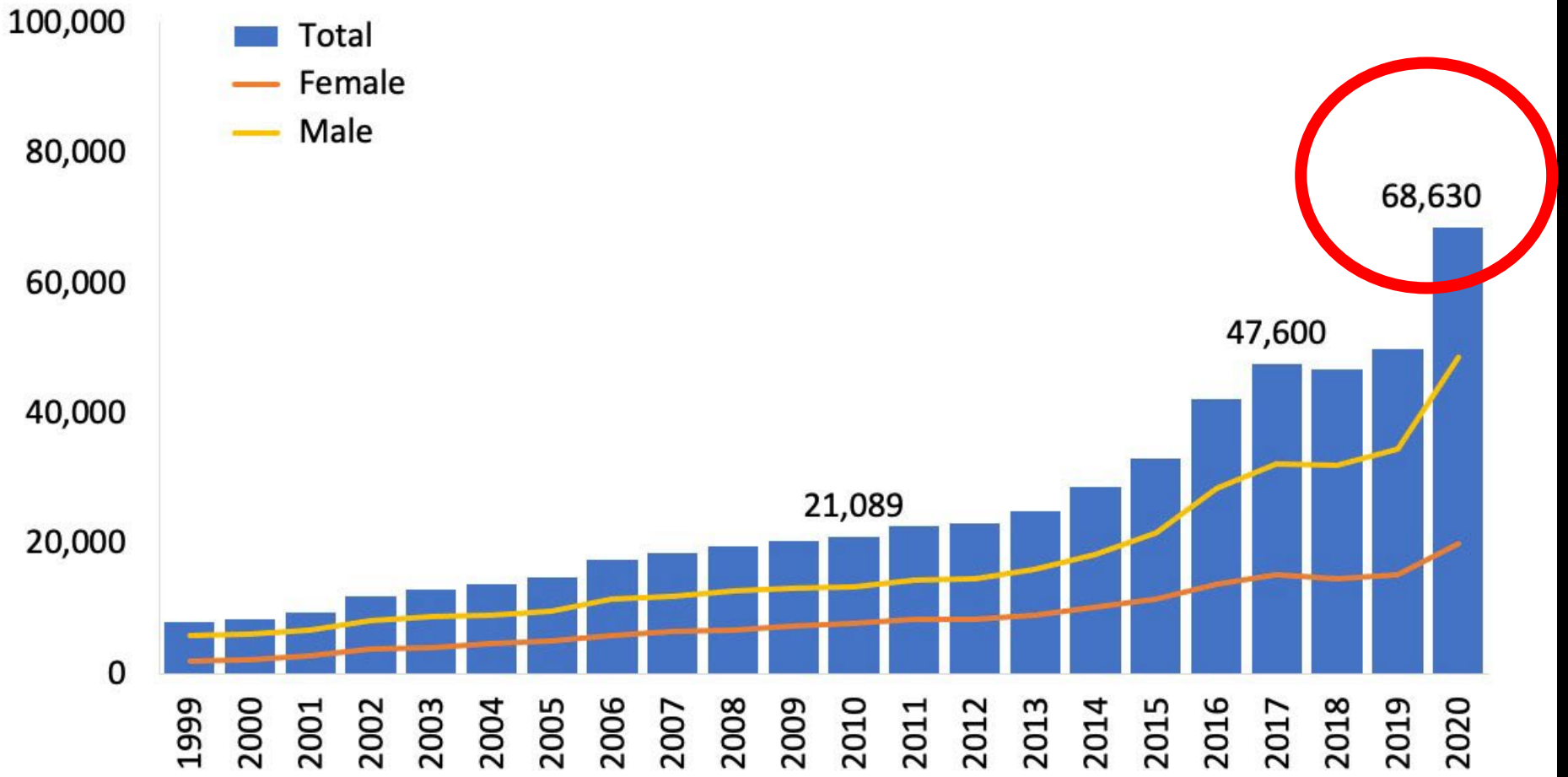
Number Among All Ages, by Gender, 1999-2020



*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.

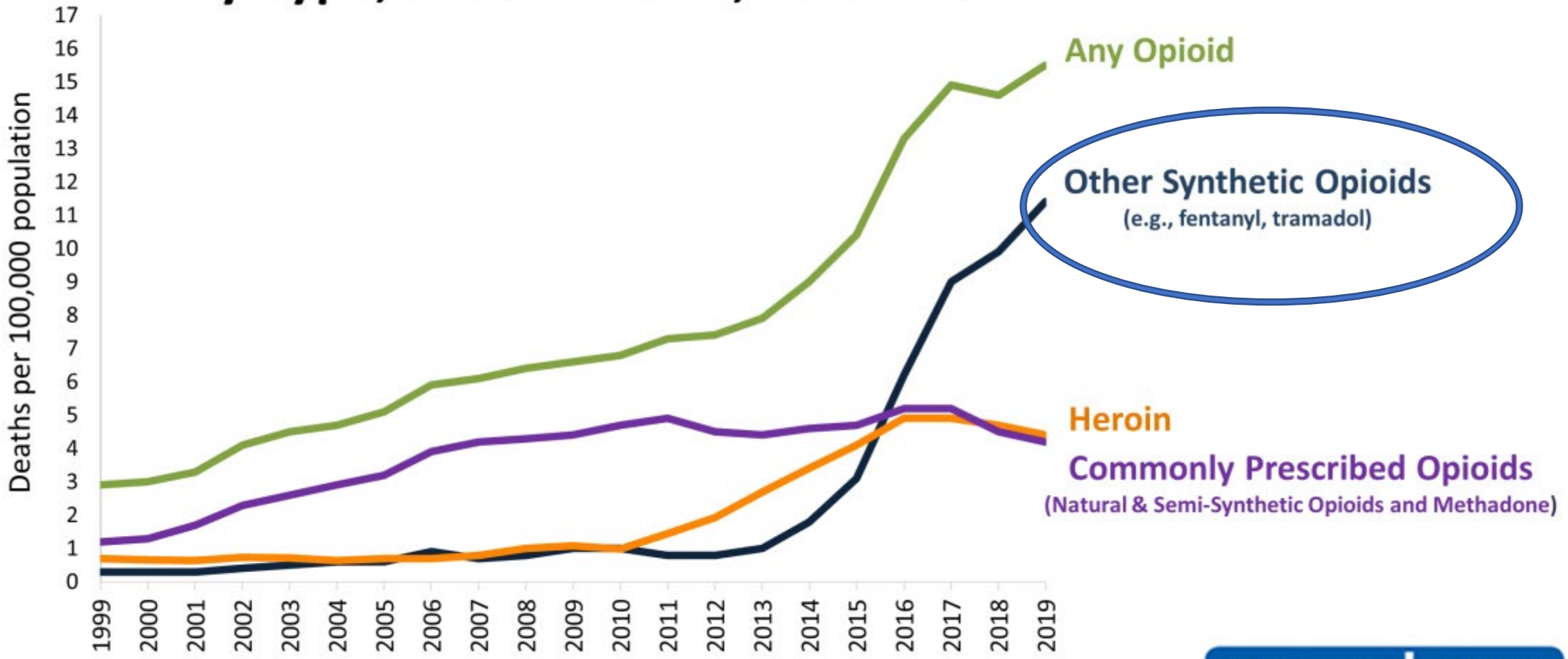
- https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates

Figure 3. National Overdose Deaths Involving Any Opioid, Number Among All Ages, by Gender, 1999-2020



*Among deaths with drug overdose as the underlying cause, the any opioid subcategory was determined by the following ICD-10 multiple cause-of-death codes: natural and semi-synthetic opioids (T40.2), methadone (T40.3), other synthetic opioids (other than methadone) (T40.4), or heroin (T40.1). 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.

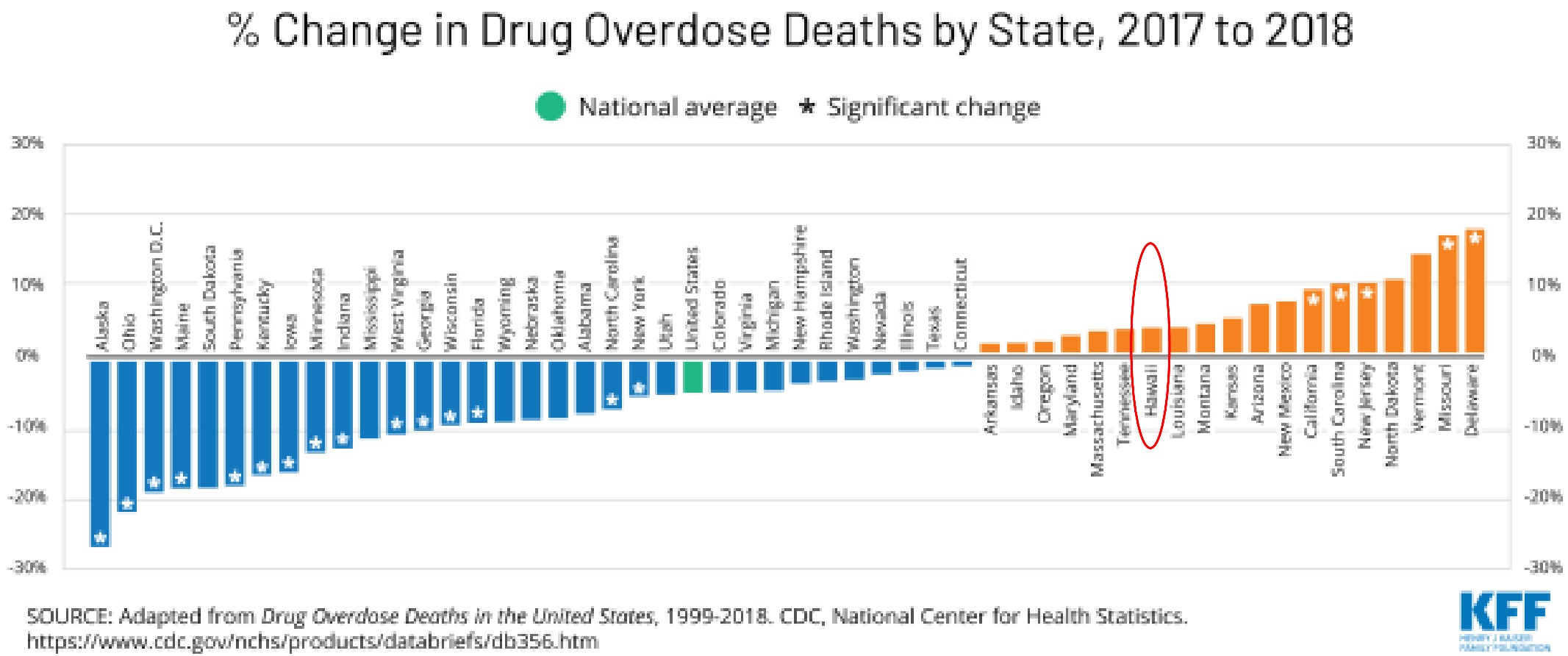
Overdose Death Rates Involving Opioids, by Type, United States, 1999-2019



SOURCE: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2020. https://wonder.cdc.gov/.

www.cdc.gov
Your Source for Credible Health Information

Drug Overdose Deaths Have Declined Nationally and in Most States, Though Some States Have Seen Increases



SOURCE: Adapted from *Drug Overdose Deaths in the United States*, 1999-2018. CDC, National Center for Health Statistics. https://www.cdc.gov/nchs/products/databriefs/db356.htm

KFF

- https://www.kff.org/other/slide/drug-overdose-deaths-have-declined-nationally-and-in-most-states-though-some-states-have-seen-increases/

Treating OUD (MAT) Medication-Assisted Treatment

- MAT - FDA approved options:
  - **Buprenorphine**
  - Methadone
  - Naltrexone
- Other option:
  - Behaviorally-Oriented Treatment

https://www.wayfair.com/rugs/pdp/red-barrel-studio-martrud-hi-im-mat-30-in-x-18-in-non-slip-outdoor-door-mat-mcrw5238.html
https://www.fda.gov/drugs/information-drug-class/information-about-medication-assisted-treatment-mat

Which of the following statement is true?

A. **Must obtain X-waiver to prescribe methadone**
B. **Must obtain X-waiver to prescribe buprenorphine**
C. **Methadone must be dispensed at OTP (opioid treatment program) clinic**
D. **Buprenorphine must be dispensed at OTP clinic**
E. **Methadone and Bup are schedule III**

Answer

Which of the following statement is true?

A. **Must obtain X-waiver to prescribe methadone**
B. **Must obtain X-waiver to prescribe buprenorphine**
C. **Methadone must be dispensed at OTP clinic**
D. **Buprenorphine must be dispensed at OTP clinic**
E. **Methadone and Bup are schedule III**

Drug Addiction Treatment Act of 2000 (DATA 2000)

- Eligible providers can now treat OUD with Buprenorphine up to 30 patients
  - https://www.federalregister.gov/documents/2021/04/28/2021-08961/practice-guidelines-for-the-administration-of-buprenorphine-for-treating-opioid-use-disorder
  - **You must still apply for X-waiver**
    - https://www.samhsa.gov/medication-assisted-treatment/become-buprenorphine-waivered-practitioner/new-practice-guidelines-faqs

Drug Addiction Treatment Act of 2000 (DATA 2000)

- To practice beyond 30 patients:
  - Eligible providers must complete the course
    - https://www.samhsa.gov/medication-assisted-treatment/find-buprenorphine-waiver-training
- Must adhere to patient panel size limits
  - 30 during the first year (whether you do training or not)
  - 100 during the second year
  - 275 during the third year

Buprenorphine - Advantage

- **(+) Ceiling Effect** due to partial agonist properties:
  - Euphoria and Resp depression effect is **much weaker** than full opioid agonists such as heroin and methadone

The ASAM Essentials of Addiction Medicine Chapter 57, P326-331, PCSSnow.org

TDH Finds Some Overdose Deaths Associated With Buprenorphine

Drug Coupled with Counseling Effective in Addiction Treatment, but Has Risk for Misuse

https://www.tn.gov/health/news/2018/1/8/tdh-finds-some-overdose-deaths-associated-with-buprenorphine.html#:~:text=TDH%20found%20a%20total%20of,can%20sometimes%20lead%20to%20death.

Monday, January 08, 2018 | 12:01pm

Total OD (2018)
1307

NASHVILLE – Buprenorphine is an important part of treatment for many with substance use disorder, and coupled with therapy and support it can save lives. However, Tennessee Department of Health data show an increase in deaths associated with buprenorphine when the drug is used with another respiratory depressant. As organizations and individuals across Tennessee work to reduce the impact of the epidemic of drug overdoses in our state, TDH is raising awareness of risks associated with buprenorphine when combined with other drugs.

TDH found a total of 67 deaths associated with buprenorphine in 2016. Most people had taken multiple drugs prior to death. However, the latest TDH analysis of drug overdose death data shows abuse of buprenorphine alone can sometimes lead to death. TDH data show ten Tennesseans only had buprenorphine present when they died between 2013 and 2016.

Retention rate: Buprenorphine vs Methadone

- Previous studies said that retention rate was better for methadone
- Current meta-analysis states retention rate is the same
  - Authors states: there were wide variation and heterogenicity among the included studies

- Hser YI, Saxon AJ, Huang D, Hasson A, Thomas C, Hillhouse M, Jacobs P, Teruya C, McLaughlin P, Wiest K, Cohen A, Ling W. Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. Addiction. 2014 Jan;109(1):79-87. doi: 10.1111/add.12333. Epub 2013 Oct 9. PMID: 23961726; PMCID: PMC3947022.
- Klimas J, Hamilton MA, Gorfinkel L, Adam A, Cullen W, Wood E. Retention in opioid agonist treatment: a rapid review and meta-analysis comparing observational studies and randomized controlled trials. Syst Rev. 2021 Aug 6;10(1):216. doi: 10.1186/s13643-021-01764-9. PMID: 34362464; PMCID: PMC8348786.

Buprenorphine - Disadvantage

- May not be sufficient to treat severe OUD
- **Need to "time" the induction: Can precipitate withdrawal** due to higher affinity to mu-opioid receptors than other full agonists
  - Naloxone in suboxone is NOT the cause for withdrawal!!

The ASAM Essentials of Addiction Medicine Chapter 57, P326-331, PCSSnow.org

CASE #1

A middle-aged woman…

- Presented to outpatient PCP clinic
- CC: requesting pain treatment
- PMH: chronic shoulder, back, hip and neck pain on prescription opioid treatment for 15 years

A middle-aged woman…

- Meds:
  - oxycodone ER 20 mg three times daily
  - oxycodone IR 10 mg every 6 hours as needed.
  - She admits taking more than she was Rx and has h/o overdosing in the past.

A middle-aged woman…

- She would typically experience opioid withdrawal symptoms of nausea, vomiting, lower extremity restlessness, anxiety, cold sweats and pain rated 6 of 10, within 6–8 hours after taking oxycodone ER.
- At times, she runs out of her meds and she would buy from a friend knowing that this can be physically hazardous.

What is her diagnosis?

A. Minor Opioid Use Disorder
B. Major Opioid Use Disorder
C. Mild Opioid Use Disorder
D. Moderate Opioid Use Disorder
E. Severe Opioid Use Disorder

HINT: She admits taking more than she was Rx and has h/o overdosing in the past. At times, she runs out and she would buy from a friend knowing that this can be physically hazardous. She experiences withdrawal.

Answer

What is her diagnosis?

A. **Minor Opioid Use Disorder**
B. **Major Opioid Use Disorder**
C. **Mild Opioid Use Disorder**
D. **Moderate Opioid Use Disorder**
E. **Severe Opioid Use Disorder**

HINT: She admits taking more than she was Rx (tolerance/ taking larger amount) and has h/o overdosing in the past. At times, she runs out and she would buy from a friend knowing that this can be physically hazardous (use knowing hazardous). She experiences withdrawal (withdrawal).

Substance Use History:

***

Tolerance: increased amount or **diminished effect**	***
Withdrawal: at least 2 s/s OR use the substance or similar substance to avoid/relieve withdrawal.	***
Number of Yes Mild (2-3) Moderate (4-5) Severe >6	***

Substance Use History:

***

Taken in **larger** amounts OR over a **longer period** than intended	***
Persistent desire OR unsuccessful effort to **cut down**	***
Great deal of **time is spent** to **obtain/use** substance or **recover** from its effect	***
Craving	***
Recurrent use resulting in **failure to do work/school/home**	***
Continued use despite of **social/interpersonal problems** from use	***
Important **activities given up**/ reduced	***
Recurrent use even in **physically hazardous**	***
Continued use despite of **knowing problems** are **caused/exacerbated** by use	***
Number of Yes Mild (2-3) Moderate (4-5) Severe >6	***

Substance Use History:

***

Taken in **larger** amounts OR over a **longer period** than intended	*** ✖
Persistent desire OR unsuccessful effort to **cut down**	***
Great deal of **time is spent** to **obtain/use** substance or **recover** from its effect	***
Craving	***
Recurrent use resulting in **failure to do work/school/home**	***
Continued use despite of **social/interpersonal problems** from use	***
Important **activities given up**/ reduced	***
Recurrent use even in **physically hazardous**	*** ✖
Continued use despite of **knowing problems** are **caused/exacerbated** by use	***
Tolerance: increased amount or **diminished effect**	*** ✖
Withdrawal: at least 2 s/s OR use the substance or similar substance to avoid/relieve withdrawal.	*** ✖
Number of Yes Mild (2-3) Moderate (4-5) Severe >6	*** 4

A middle-aged woman…

- Physical exam was unremarkable.
- UDS: (+) for oxycodone, (+) for hydrocodone, (+) for opiate
- Initial Clinical Opiate Withdrawal Score (COWS) was 0.

COWS

Clinical opiate withdrawal scale

COWS

- 11-item scale designed to be administered by a clinician.
- Can be used for both inpatient and outpatient settings.
- Objectives: HR, Pupil size, Piloerection
- Subjective: restlessness, aches, tremor, anxiety
- Either or (can fake / non-specific): sweating (subjective included), GI upset (pain included), yawning, tearing/ runny nose

Resting Pulse Rate: _____beats/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	**GI Upset**: *over last 1/2 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 1/2 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 or 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 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerrection
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

https://nida.nih.gov/sites/default/files/ClinicalOpiateWithdrawalScale.pdf

OOWS

- **Objective** Opioid Withdrawal Scale
- Useful in office or inpatient setting.
- Objective findings only
- Observe patient for **FIVE minutes**
- >/= 3 points → px is ready for induction

- Gossop M. The development of a Short Opiate Withdrawal Scale (SOWS). Addict Behav. 1990;15(5):487-90. PMID: 2248123
- Bradley BP, Gossop M, Phillips GT, Legarda JJ. The development of an opiate withdrawal scale (OWS). Br J Addict. 1987 Oct;82(10):1139-42. PMID: 3479162
- Handelsman L, Cochrane KJ, Aronson MJ, Ness R, Rubinstein KJ, Kanof PD. Two new rating scales for opiate withdrawal. Am J Drug Alcohol Abuse. 1987;13(3):293-308. PMID: 3687892
- https://medicine.yale.edu/sbirt/Images/OOWS_tcm508-251773.pdf
- file:///C:/Users/18083/Downloads/OOWS.pdf

Yawning	0 = no yawns , 1 = ≥ 1 yawn 2
Rhinorrhea	0 = < 3 sniffs , 1 = ≥ 3 sniffs
Piloerection (observe arm)	0 = absent, 1 = present
Perspiration	0 = absent, 1 = present
Lacrimation	0 = absent , 1 = present
Tremor (hands)	0 = absent, 1 = present
Mydriasis	0 = absent, 1 = ≥ 3 mm
Hot and Cold flushes	0 = absent, 1 = **shivering / huddling for warmth**
Restlessness	0 = absent, 1 = **frequent shifts of position**
Vomiting	0 = absent, 1 = present
Muscle twitches	0 = absent, 1 = present
Abdominal cramps	0 = absent, 1 = **Holding stomach**
Anxiety	0 = absent, 1 = mild - severe **(finger tapping, fidgeting, agitation)**

A middle-aged woman…

- After extensive counseling and discussion, the patient opted for unobserved buprenorphine induction at home.
- She was given education about home buprenorphine induction

Induction at home??

Review: Traditional Buprenorphine induction

- Done **under clinical supervision**
- Pt to hold all opioids prior to the visit and COWS to be 6 or more (some states 12 or more), if not, need to reschedule induction
  - The recommended period of abstinence can range from 12 to 16 hours for short-acting opioids such as hydromorphone or diacetylmorphine (heroin)
- Day 1: Start 2-4mg, give q 2hours, max dose 8-12mg on the first day
- Day 2: take dose from day 1 + alpha - max dose 12-16mg
- Day 3: As above with max dose of 16mg-24mg

- Buprenorphine SL Traditional Induction SAMHSA. Tip 63. Medications for opioid use disorder. 2018 Casadonte PP, et al. Buprenorphine Induction. Providers' clinical support system for medication assisted treatment, 2013
- https://www.asam.org/docs/default-source/education-docs/clinic-induction-protocol-example_it-matttrs_8-28-2017.pdf?sfvrsn=a30640c2_2

Home Buprenorphine/Naloxone Induction in Primary Care

Joshua D. Lee, MD MSc[1,2], Ellie Grossman, MD MPH[1], Danae DiRocco, MPH[1], and Marc N. Gourevitch, MD MPH[1]

[1]New York University School of Medicine, New York, NY, USA; [2] New York, NY, USA.

- Induction on 103 patients
- Induction complications similar rate to office induction
- Not associated with short-term treatment drop out

Some interesting fact

- Telephone support was used **infrequently:** 17 px only
  - Phone call was **3-4 min**
  - Usually px reporting their **induction experience**

Home induction is commonly practiced now, even here in Hawaii

Despite being safe…

Canadian study

RESEARCH Open Access

Buprenorphine unobserved "home" induction: a survey of Ontario's addiction physicians

Anita Srivastava*, Meldon Kahan, Pamela Leece and Alison McAndrew

Abstract

Background: Ontario patients on opioid agonist treatment (OAT) are often prescribed methadone instead of buprenorphine, despite the latter's superior safety profile. Ontario OAT providers were surveyed to better understand their attitudes towards buprenorphine and potential barriers to its use, including the induction process.

Methods: We used a convenience sample from an annual provincial conference to which Ontario physicians who are involved with OAT are invited.

Results: Based on 85 survey respondents (out of 215 attendees), only 4% of Ontario addiction physicians involved in OAT routinely used unobserved "home" buprenorphine induction: 59% of physicians felt that unobserved induction was risky because it was against "the guidelines" and 66% and 61% respectively believed that unobserved "home" induction increased the risk of diversion and of precipitated withdrawal.

Conclusions: Ontario addiction physicians largely report following the traditional method of bringing in patients for observed in-office buprenorphine induction; they expressed fear of precipitated withdrawal, diversion, and going against clinical guidelines. The hesitance in using unobserved induction may explain, in part, Ontario's reliance on methadone.

Keywords: Buprenorphine, Physician survey, Home induction, Unobserved

In US…

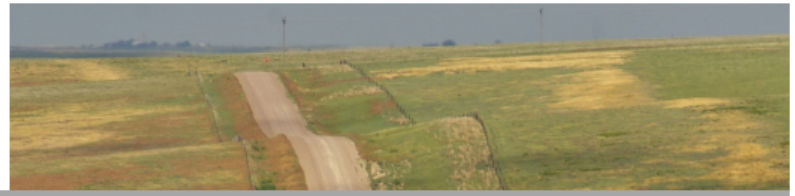
- Although home induction is more common, consensus / guidelines recommend directly observed initial dosing followed by multiple in-clinic visits during the induction week.

- ASAM now has step by step guide to “unobserved home induction”
  - https://www.asam.org/docs/default-source/education-docs/unobserved-home-induction-patient-guide.pdf?sfvrsn=16224bc2_0

A middle-aged woman…

- She was instructed using ASAM protocol:
- She was instructed to take first dose of buprenorphine–naloxone (4–1 mg) when she entered moderate withdrawal based on self-assessment of withdrawal symptoms.
- Instructed to take another 4–1 mg in 1 hour if she did not have improvement in her withdrawal symptoms.

IT MATTTRs™



A Patient's Guide to Starting Buprenorphine at Home

PREPARATION

Receiving Medication Assisted Treatment (MAT) with Buprenorphone

Medication assisted treatment (MAT) with buprenorphine is a safe and effective method to help people with an opioid use disorder stop using prescription pain medications, heroin, and other opioids. There are three main phases of MAT: induction (first 1-2 days), stabilization (several weeks), and maintenance (as long as it takes). Before you start treatment, be sure to talk with your health care provider about your plans for treatment.

Your care team should schedule an MAT Procedure Review Appointment with you. This is a great time to discuss your decision to receive MAT, your goals and motivations, concerns, and receive important information. Before starting treatment, your health care team will also conduct a physical evaluation and some lab tests.

Home or Doctor's Office?

This process of getting started on buprenorphine is called Induction. You can be at your doctor's office to get started, or you can do this at home. Talk with your doctor and care team about which option is better for you. There are pros and cons for both options. Which option do you prefer?

DAY 1

Checklist

Check the boxes next to each step to help you track your progress. Be patient — you're close to feeling better!

Before taking your first dose, stop taking all opioids for 12-36 hours. You should feel pretty lousy, like having the flu. These symptoms are normal. You will feel better soon.

- ❑ Before your first dose of medication, you should feel **at least three** of the following:
  - ○ Very restless, can't sit still
  - ○ Twitching, tremors, or shaking
  - ○ Enlarged pupils
  - ○ Bad chills or sweating
  - ○ Heavy yawning
  - ○ Joint and bone aches
  - ○ Runny nose, tears in your eyes
  - ○ Goose flesh (or goose bumps)
  - ○ Cramps, nausea, vomiting or diarrhea
  - ○ Anxious or irritable
- ❑ Complete the SOWS. You need your SOWS score to be ≥17 before taking your first dose of buprenorphine.

Schedule

- ❑ **Take 4 mg** of buprenorphine under the tongue (tablet or film strip). (Half of an 8 mg tablet, or two 2 mg tablets). Usually one film strip.
- ❑ Put the tablet or film under your tongue. Do not swallow it. Buprenorphine does not work if swallowed.
- ❑ Wait an hour.
  - – If you feel fine, do not take any more medication today. Record your total for the day dose below.
  - – If you continue to have withdrawal symptoms, take a second dose under your tongue (4 mg).

https://www.asam.org/docs/default-source/education-docs/unobserved-home-induction-patient-guide.pdf?sfvrsn=16224bc2_0

SOWS

- Subjective Opiate Withdrawal Scale
- Scores from 0-4
- Must be score of 17 or higher to start

- https://www.asam.org/docs/default-source/education-docs/sows_8-28-2017.pdf

Name: _____

DOB: _____

IT ATTTRs Colorado

Subjective Opiate Withdrawal Scale (SOWS)

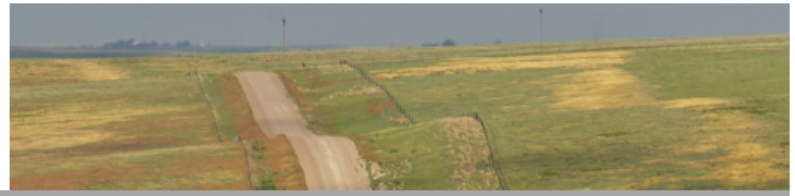
Instructions: We want to know how you're feeling. In the column below today's date and time, use the scale to write in a number from 0-4 about how you feel about each symptom right now.

Scale: 0 = not at all 1 = a little 2 = moderately 3 = quite a bit 4 = extremely

DATE						
TIME						
SYMPTOM		SCORE	SCORE	SCORE	SCORE	SCORE
1	I feel anxious					
2	I feel like yawning					
3	I am perspiring					
4	My eyes are tearing					
5	My nose is running					
6	I have goosebumps					
7	I am shaking					
8	I have hot flushes					
9	I have cold flushes					
10	My bones and muscles ache					
11	I feel restless					
12	I feel nauseous					
13	I feel like vomiting					
14	My muscles twitch					
15	I have stomach cramps					
16	I feel like using now					
TOTAL						

Mild Withdrawal = score of 1 – 10
Moderate withdrawal = 11 – 20
Severe withdrawal = 21 – 30

IT MATTTRs™



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https://www.asam.org/docs/default-source/education-docs/unobserved-home-induction-patient-guide.pdf?sfvrsn=16224bc2_0

Day of Home induction….

- She waited almost a full day from her last oxycodone and experienced moderate withdrawal symptoms.
- Took initial 4-1 mg → she experienced worsening of her withdrawal symptoms including:
  - increase in anxiety, sweatiness, restless legs, chills and pain ‘all over’.
    - FYI: ASAM guidelines states to “call” the provider for possible precipitated withdrawal… ☺

Day of Home induction….

- She didn’t call…
- She waited 30 minutes and took another dose of 4–1 mg (total 8-2mg)
- She **felt worse** instead of improving → called the clinic (2hrs into induction)

Day of Home induction….

- The clinic instructed her to take another 8-2mg and 1g of Tylenol (total 16mg)
  - ASAM guideline allows patients to take max 16mg on the 1st day
  - It also instructs patient to CALL if still (+) s/s after taking 16 mg
- Her symptoms worsened → instructed her to come to ED.

Now in ED…

- The patient is tearful, appeared miserable and complained of…
  - Hot and cold flushes
  - Achy all over
  - LBM at home
  - Restless legs

In ED…

- Her vital signs were normal.
- On exam, she was irritable and had…
  - Pupils: 5 mm dilated pupils, (+) lacrimation
  - Skin: (+) Piloerection
  - Ext: frequent extraneous movements of her legs
- Her COWS was 25.

What is going on?

A. Buprenorphine overdose
B. Buprenorphine toxicity
C. Buprenorphine induced anxiety
D. Buprenorphine induced withdrawal
E. Buprenorphine underdose

Answer

What is going on?

A. Buprenorphine overdose
B. Buprenorphine toxicity
C. Buprenorphine induced anxiety
D. Buprenorphine induced withdrawal
E. Buprenorphine underdose

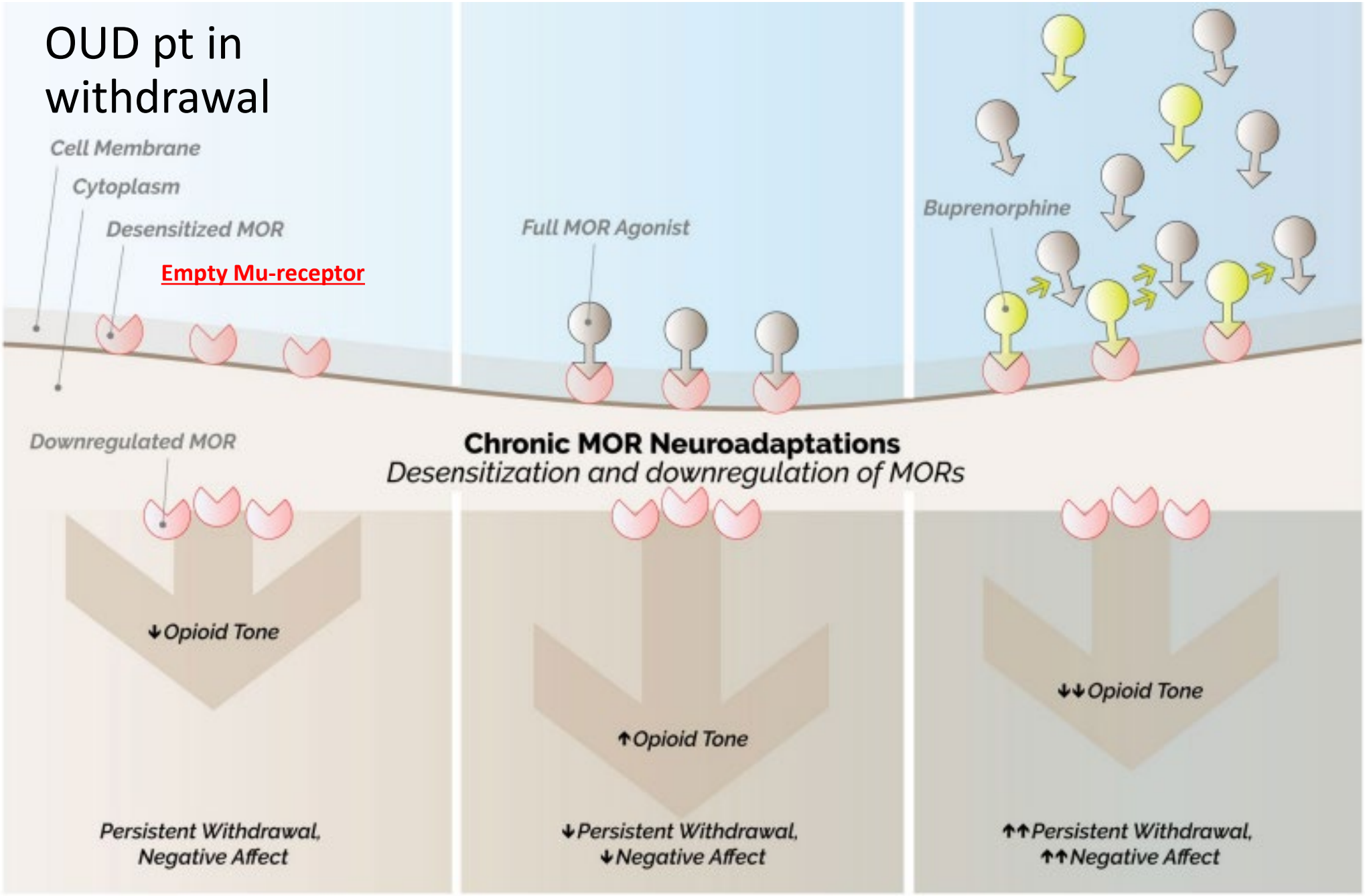
What is precipitated withdrawal?

Precipitated opioid withdrawal

- Rapid onset of opioid withdrawal symptoms following the first dose of buprenorphine
- Gradually subsides over the subsequent 6–24 h.
- Well-recognized adverse outcome:
  - Whitley et al., 16.8% had complicated induction and out of 16.8%, 55.8% had precipitated withdrawal (hence ~ 9% had precipitated withdrawal).
    - Risk factors for precipitated withdrawal include
      - transferring from long-acting opioids (methadone)
      - recent benzodiazepine use
      - no past patient experience with buprenorphine
      - a low initial dose of buprenorphine/naloxone
- Complicated inductions were significantly associated with treatment outcomes, as patients with complicated inductions had lower 30-day retention rates than those with routine inductions.

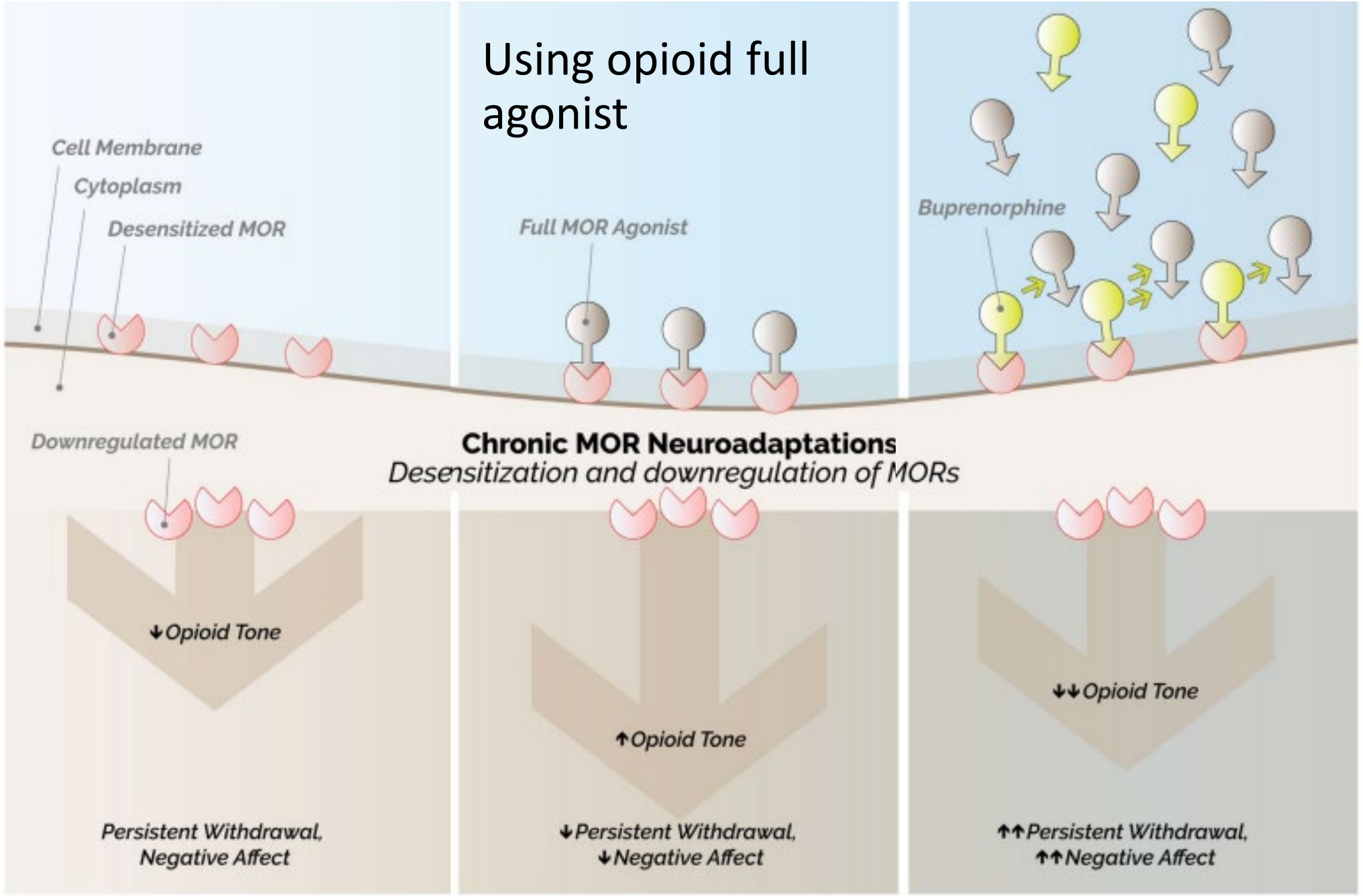
- Whitley SD, Sohler NL, Kunins HV, Giovanniello A, Li X, Sacajiu G, Cunningham CO. Factors associated with complicated buprenorphine inductions. J Subst Abuse Treat. 2010 Jul;39(1):51-7. doi: 10.1016/j.jsat.2010.04.001. PMID: 20682186; PMCID: PMC4755478.

OUD pt in withdrawal

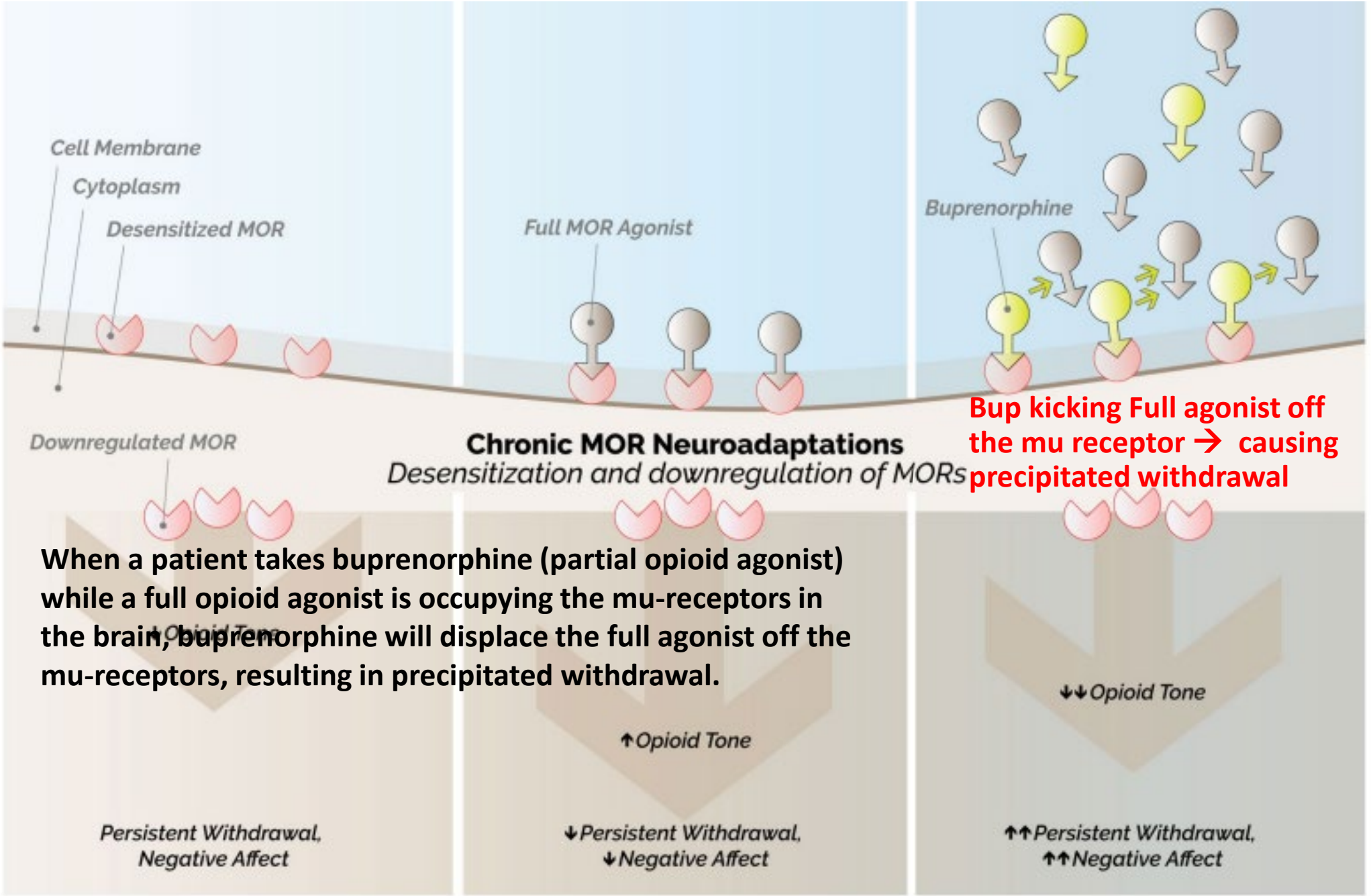


De Aquino, J.P., Parida, S. & Sofuoglu, M. The Pharmacology of Buprenorphine Microinduction for Opioid Use Disorder. *Clin Drug Investig* **41,** 425–436 (2021). https://doi.org/10.1007/s40261-021-01032-7

Using opioid full agonist



De Aquino, J.P., Parida, S. & Sofuoglu, M. The Pharmacology of Buprenorphine Microinduction for Opioid Use Disorder. *Clin Drug Investig* **41,** 425–436 (2021). https://doi.org/10.1007/s40261-021-01032-7



Bup kicking Full agonist off the mu receptor → causing precipitated withdrawal

When a patient takes buprenorphine (partial opioid agonist) while a full opioid agonist is occupying the mu-receptors in the brain, buprenorphine will displace the full agonist off the mu-receptors, resulting in precipitated withdrawal.

De Aquino, J.P., Parida, S. & Sofuoglu, M. The Pharmacology of Buprenorphine Microinduction for Opioid Use Disorder. *Clin Drug Investig* **41,** 425–436 (2021). https://doi.org/10.1007/s40261-021-01032-7

Treating precipitated withdrawal

- 3 Potential responses to precipitated withdrawal:
  - 1. reassurance and symptomatic medication (e.g. anti-emetics, anti-inflammatories, sedatives)
  - 2. adding further buprenorphine to increase opioid agonist effect
  - 3. abandon buprenorphine treatment (re-induce at later day) or reverting to treatment with full opioid agonists, such as methadone
- Clinical experience suggests that once a patient experience precipitated withdrawal, they are reluctant to undergo re-induction

- Oakley B, Wilson H, Hayes V, Lintzeris N. Managing opioid withdrawal precipitated by buprenorphine with buprenorphine. Drug Alcohol Rev. 2021; 40(4): 567–71.

Treating precipitated withdrawal

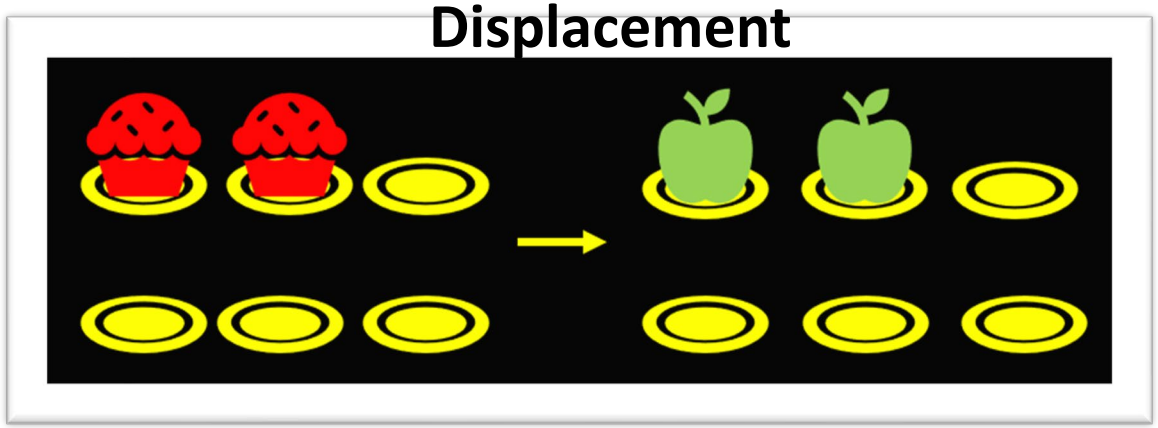
- Current guidelines (2021) suggest further buprenorphine doses, however the recommendations are low doses (2mg every 1-2 hours) and potentially prolong precipitated withdrawal.

- https://pcssnow.org/wp-content/uploads/2021/12/PCSS-GuidanceBuprenorphineInduction.Casadonte.pdf

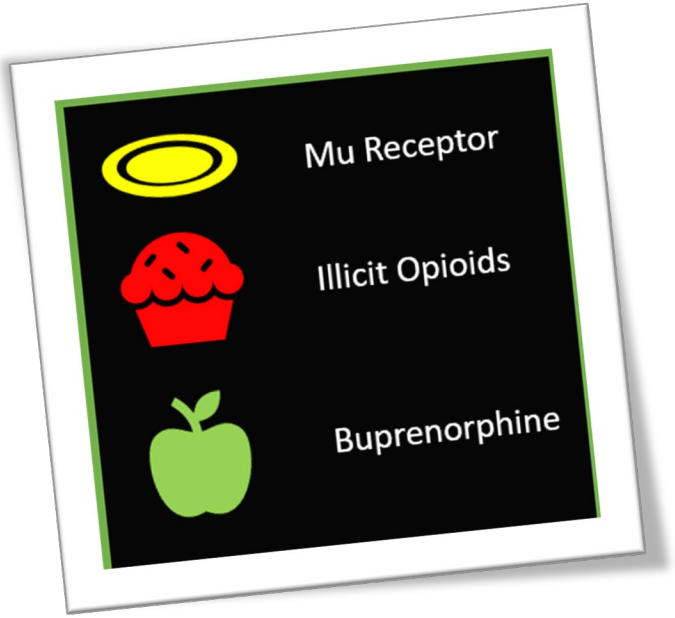
- Recent literature shows that precipitated withdrawal symptoms are quickly reversible with rapid administration of a **high dose** of buprenorphine by saturating the mu-receptors.

- Oakley B, Wilson H, Hayes V, Lintzeris N. Managing opioid withdrawal precipitated by buprenorphine with buprenorphine. Drug Alcohol Rev. 2021; 40(4): 567–71.

Rational: Treating precipitated withdrawal

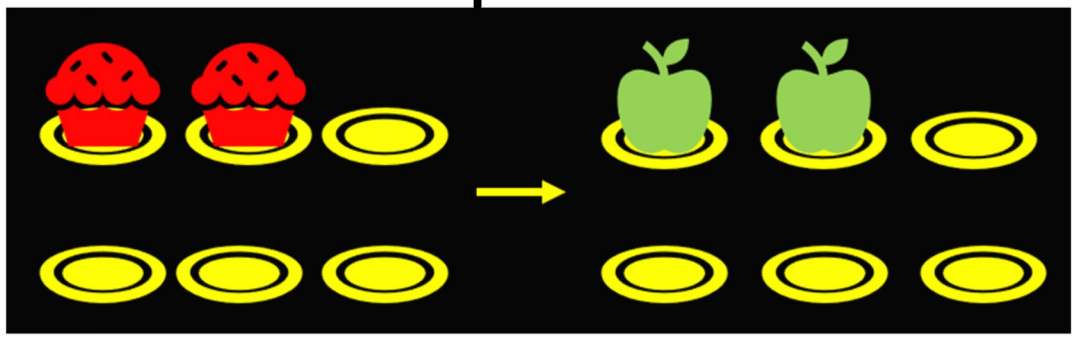


→ **Precipitated Withdrawal**

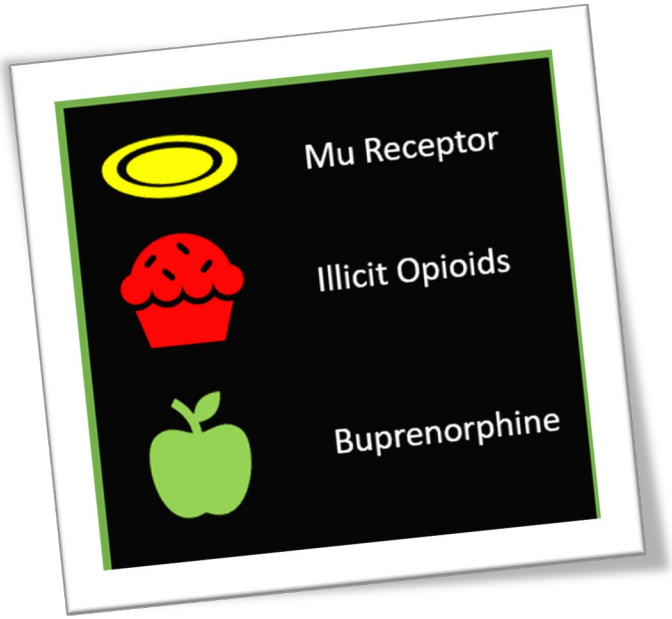


Rational: Treating precipitated withdrawal

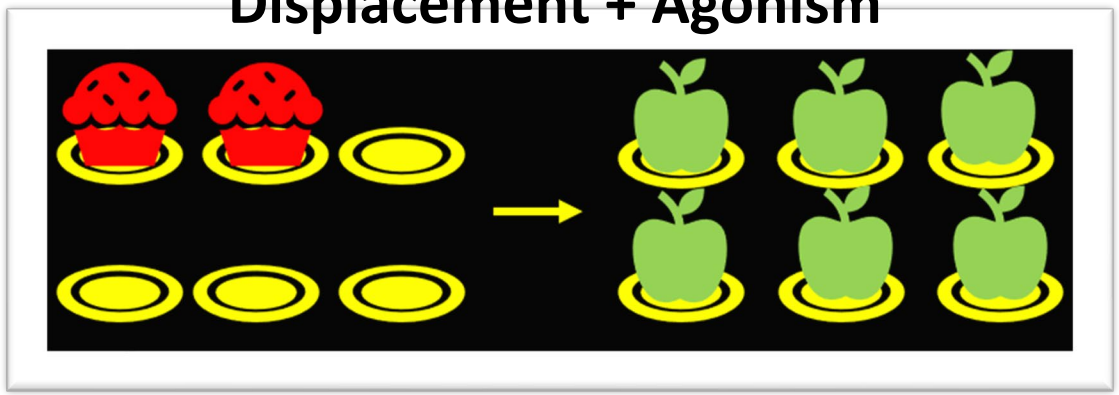
Displacement



→ **Precipitated Withdrawal**



Displacement + Agonism

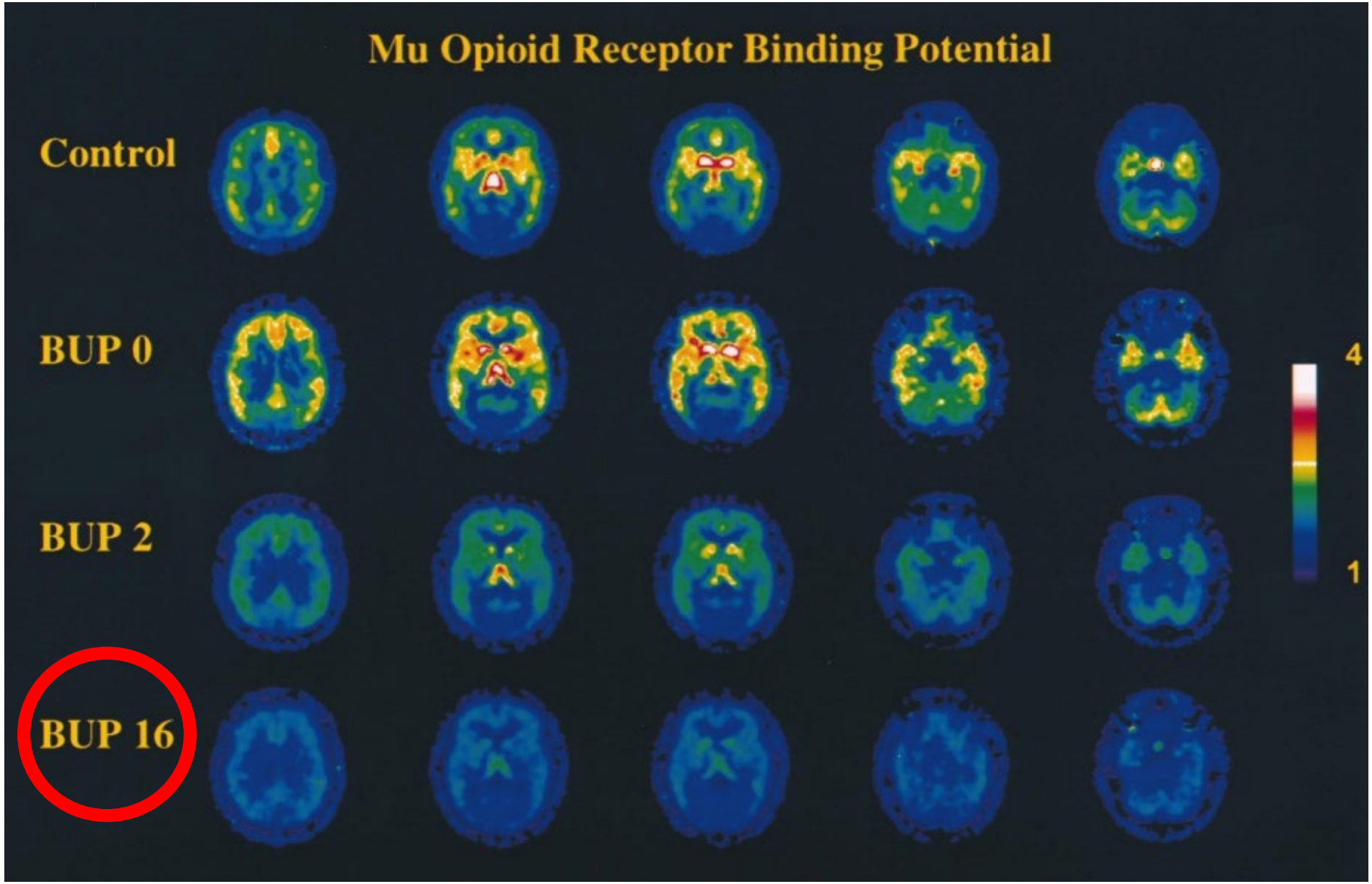


→ **Relief**

Zubieta, JK., Greenwald, M., Lombardi, U. *et al.* Buprenorphine-Induced Changes in Mu-Opioid Receptor Availability in Male Heroin-Dependent Volunteers: A Preliminary Study. *Neuropsychopharmacol* **23,** 326–334 (2000). https://doi.org/10.1016/S0893-133X(00)00110-X

Foster B, Twycross R, Mihalyo M, Wilcock A. Buprenorphine. J Pain Symptom Manage 2013; 45(5): 939–49

- Studies show showed that 16 mg of buprenorphine occupies majority of mu-receptors in the brain
  - ~ 80% - 95%
- Control: non- heroin user
- Bup 0: Heroin user
- Bup 2: 2mg → 35-50% reduction in availability
- Bup 16: 16mg (79-95% reduction in availability) → Barely NO receptor available



Rational: Treating precipitated withdrawal

- Therefore theoretically, by giving a high dose of buprenorphine, precipitated withdrawal can be reversed as the brain gets oversaturated with buprenorphine.

Going back to the case…still in ED

- **Review:** Pt took 16mg total, still in withdrawal, now in ED, COWS 25
- In ED, patient got another 2–0.5 mg of buprenorphine-naloxone
  - Now total 18-4.5mg
  - One hour later, the patient’s COWS score improved to 13.

She is now admitted

- She was admitted under observation
- She took another dose of 2–0.5 mg (total 20-5mg) on the day of induction.

Going back to the case…still in ED

- On the next hospital day, the patient's COWS was 0.
- Patient was subsequently discharged later that day with a COWS score of 0 on a total daily buprenorphine dose of 20 mg.

Patient NOW...

- Five months after induction, the patient continues to follow up at the clinic and is currently doing well on 16–4 mg of buprenorphine-naloxone daily.

She describes her experience with precipitated withdrawal, she stated that the day of induction felt…

‘like a whole week, like an eternity, like it would last forever but it’s not’

and recommends (others) to…

‘stick it out because it is worth it’.

Currently, the patient is doing well – no cravings and states….

“feels like a brand new person!”

But… why did she get into precipitated withdrawal??

She was in withdrawal PRIOR to taking the 1st dose…

- Although we cannot completely rule out the possibility that she did not follow the induction instructions…
- We suspect our patient's experience with induction and precipitated withdrawal occurred due to the **presence of additional opioids** in her system besides oxycodone.

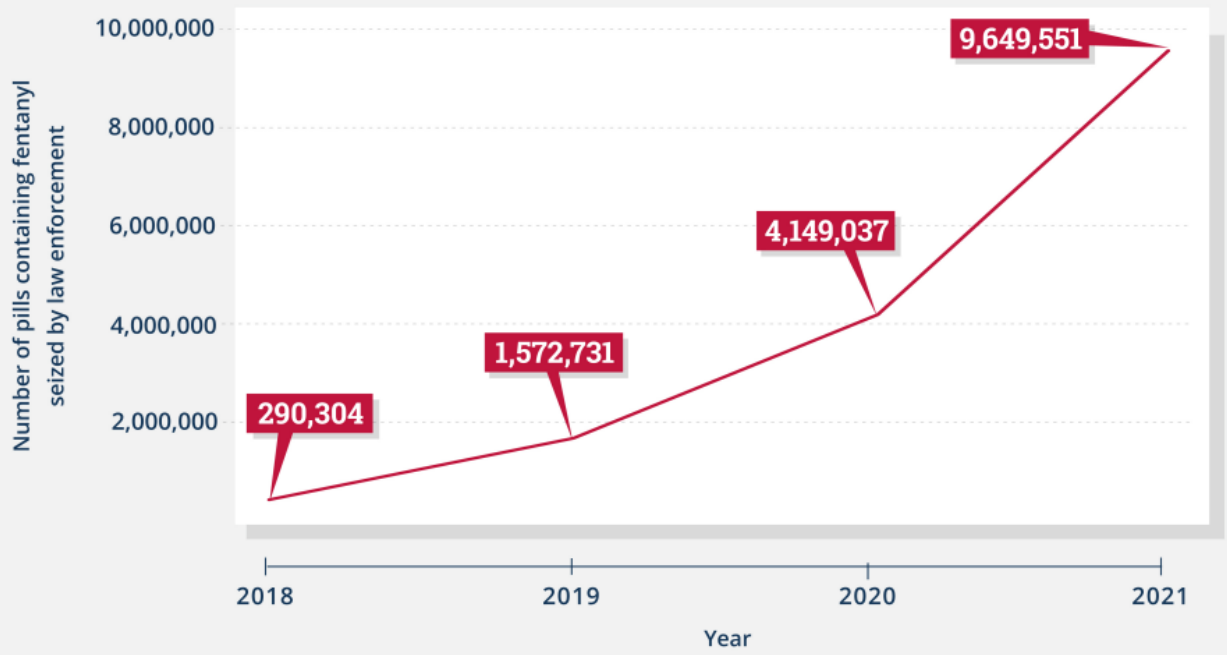
- National Institute on Drug Abuse. Fentanyl Drug Facts. National Institute on Drug Abuse. Published 28 February 2019. https://www.drugabuse.gov/ publications/drugfacts/fentanyl (accessed on 29 April 2021).

Possible substance:

- Fentanyl is a synthetic opioid
- 50-100 times stronger than morphine.
- Many illicit drugs are contaminated with fentanyl (to increase potency), which plays a major part in deaths due to drug use
- Illicit Fentanyl is primarily manufactured in Mexico.

National Institute on Drug Abuse: Fentanyl DrugFacts. Available from: https://www.drugabuse.gov/publications/drugfacts/fentanyl

Number of Pills Containing Fentanyl Seized by Law Enforcement in the United States, 2018 – 2021



Estimates based on data reported by the Office of National Drug Control Policy's High Intensity Drug Trafficking Areas program

Reference: JJ Palamar, et al. *Drug and Alcohol Dependence.* DOI: 10.1016/j.drugalcdep.2022.109398 (2022)

NIH National Institute on Drug Abuse

nida.nih.gov

She did report **buying oxycodone from a friend**

- Her **UDS was positive** for hydrocodone and opiates, which she denied knowingly taking.
  - This raised suspicion that the 'oxycodone' she bought was **laced with other substances**
  - The Drug Enforcement Agency (DEA) recently issued a warning about fentanyl-laced drugs
  - Hawaii Intensity Drug Trafficking Area officers **have confirmed** that counterfeit oxycodone laced with fentanyl has been appearing in our local area
- Fentanyl unfortunately is **not detected by our standard UDS assay** and was not obtained in this case.

- National Institute on Drug Abuse. Fentanyl Drug Facts. National Institute on Drug Abuse. Published 28 February 2019. https://www.drugabuse.gov/publications/drugfacts/fentanyl (accessed on 29 April 2021).
- Alarming Spike in Fentanyl-Related Overdose Deaths Leads Officials to Issue Public Warning. https://www.dea.gov/press-releases/2020/08/06/ alarming-spike-fentanyl-related-overdose-deaths-leads-officials-issue (accessed on 29 April 2021).
- Hawai'i High Intensity Drug Trafficking Area (HIDTA). Fentanyl, Counterfeit Oxycodone. December 2020

So what does fentanyl got to do with precipitated withdrawal?

- There is **increased incidence of precipitated withdrawal** during buprenorphine induction in patient abusing illicit fentanyl **who are in moderate to severe withdrawal** at the time of induction.
- This phenomena is thought to occur due to the **lipophilic nature** of fentanyl resulting in increased volume of distribution and slow dissipation due to prolonged use.
  - In Huhn ,et al., **protracted renal clearance** of fentanyl has been observed where mean renal clearance time for fentanyl in OUD patients consistently longer than clearance of other short-acting opioids.
  - In this study, the mean clearance is **approximately two weeks**, but might take four weeks or longer in chronic fentanyl users.

- Huhn AS, Hobelmann JG, Oyler GA, Strain EC. Protracted renal clearance of fentanyl in persons with opioid use disorder. Drug Alcohol Depend. 2020 Sep 1;214:108147. doi: 10.1016/j.drugalcdep.2020.108147. Epub 2020 Jul 2. PMID: 32650192; PMCID: PMC7594258.
- Randhawa PA, Brar R, Nolan S. Buprenorphine–naloxone "microdosing": an alternative induction approach for the treatment of opioid use disorder in the wake of North America's increasingly potent illicit drug market. CMAJ 2020; 192(3): E73.

What can we do?

- The emergence of non-pharmaceutical fentanyl raises additional concerns for complicated induction given it is lipophilic with a large body of distribution.
- Different induction has been tried:
  - Micro-dosing: avoids withdrawal while continuing full opioid agonist therapy; however, it takes ~7 days for induction.
  - Macro-dosing (aka: single large dose buprenorphine induction): can ALSO avoid precipitating withdrawal by providing a sufficient dose to occupy available receptors
    - Rational: 16 mg of buprenorphine occupies between 80-91% of mu opioid receptors, and opioid withdrawal occurs when less than 50% of receptors are occupied.

Conclusion from Case #1:

- Rapid administration of buprenorphine treats buprenorphine-precipitated withdrawal well - giving a high dose of buprenorphine is safe and will allow rapid reversal of the withdrawal symptoms.
- With the rising prevalence of fentanyl-laced drugs, instances of precipitated withdrawal are likely to continue…so don’t panic!

Case #2: Microdosing…

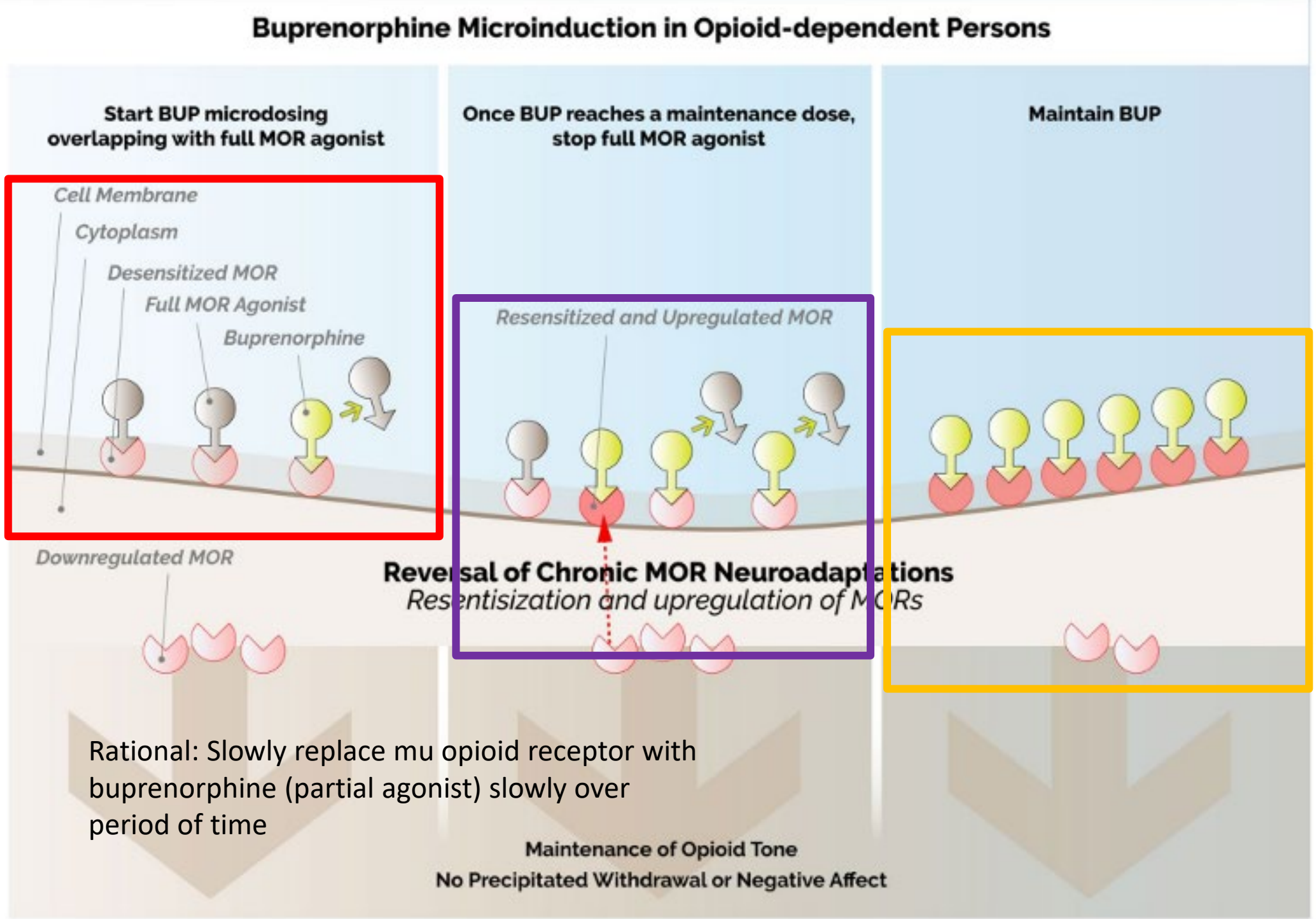
What is Microdosing / Microinduction?

- Microinduction (aka microdosing) is a novel approach
- Possible way to get around traditional prolonged opioid tapers, and reduce the risk of precipitated withdrawal
- Barriers to traditional buprenorphine induction:
  - Need to experience opioid withdrawal prior to induction
  - Precipitated withdrawal is worse than regular withdrawal

De Aquino, J.P., Parida, S. & Sofuoglu, M. The Pharmacology of Buprenorphine Microinduction for Opioid Use Disorder. *Clin Drug Investig* **41,** 425–436 (2021). https://doi.org/10.1007/s40261-021-01032-7

What is microdosing?

- AKA Randhawa method
- Microdosing involves prescribing buprenorphine–naloxone in a small initial dose with incremental increases to both dose and frequency over time.
- Opioids are allowed with current use until day 7
- Day 1: 0.5mg/0.125mg once a day
- Day 2: 0.5mg/0.125mg twice a day
- Day 3: 1mg/0.25mg twice a day
- Day 4: 2mg/0.5mg twice a day
- Day 5: 3mg/1mg twice a day
- Day 6: 4mg/2mg twice a day
- Day 7: 12mg Daily – Stop opioids
- Randhawa, Privia A et al. “Buprenorphine-naloxone "microdosing": an alternative induction approach for the treatment of opioid use disorder in the wake of North America's increasingly potent illicit drug market.” *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* vol. 192,3 (2020): E73. doi:10.1503/cmaj.74018


Buprenorphine Microinduction in Opioid-dependent Persons
Start BUP microdosing overlapping with full MOR agonist
Once BUP reaches a maintenance dose, stop full MOR agonist
Maintain BUP
Cell Membrane
Cytoplasm
Desensitized MOR
Full MOR Agonist
Buprenorphine
Resensitized and Upregulated MOR
Downregulated MOR
Reversal of Chronic MOR Neuroadaptations
Resentisization and upregulation of MORs
Rational: Slowly replace mu opioid receptor with buprenorphine (partial agonist) slowly over period of time
Maintenance of Opioid Tone
No Precipitated Withdrawal or Negative Affect

When and why do we use microdosing?

These are new methods and no consensus yet…but, appeared to be

- Useful to convert from long acting opioid to buprenorphine (i.e. methadone)
  - Studies show higher rate of subjective complaints of experiencing "withdrawal" reported by patients who were switched from methadone to buprenorphine in traditional induction
- Useful in very anxious patient who is terrified of withdrawal
- Useful in fentanyl users (i.e. case #1)
- **MAYBE:** Useful in pregnancy: currently in HI, patients are hospitalized for suboxone induction
  - 1st trimester → opioid withdrawal can increase risk of miscarriage
  - 3rd trimester → opioid withdrawal can increase risk of preterm labor
- **Lastly, useful in patient with ACUTE pain who requires full agonist**

Case #2
Female in her 50s…

- CC: back pain
- PMH: lumbar osteomyelitis of the spine with epidural abscess which she left AMA multiple times, anxiety, severe opioid use disorder w/ remote, h/o being on suboxone
- SH: Daily heroin user (IVDU)

Case #2
Female in her 50s…

- Pt was placed on antibiotics.
- 1 week later, she underwent back surgery.
- Antibiotics were continued
- Acute pain was managed by pain and palliative with full opioid agonist (hydromorphone and IV morphine)

Case #2
Female in her 50s…

- Due to anxiety, patient had hard time coming down on the full agonist opioid. Staff had difficult time with the patient.
- After 3+ weeks, patient's IV morphine was came down per staff's cooperation from 4mg to 2mg to 1mg to now 0.5mg IV q4 PRN but couldn't come down on hydromorphone.

Case #2
Female in her 50s…

- When addiction medicine team saw the patient, patient admitted that her pain is worse when her “heart” (emotion) hurts.
- Pt told the team that her ultimate goal is to be BACK on buprenorphine treatment.
- Microdosing was discussed. Pt was reluctant.
- After ~ 1 week, pt agreed.

Case #2 Microdosing

Day	Buprenorphine (total)	Total PO hydromorphone (4mg q4 PRN)	Total IV morphine (0.5mg q4 PRN)	Randhawa
1	0.5mg qd (0.5mg)	20mg	2.5mg	0.5mg qd (0.5mg)
2	0.5mg bid (1mg)	24mg	2.5mg	0.5mg bid (1mg)
3	1mg bid (2mg)	24mg	2.5mg	1mg bid (2mg)
4	2mg bid (4mg)	16mg	3mg	2mg bid (4mg)
5	3mg bid (6mg)	20mg	2.5mg	3mg bid (6mg)
6	4mg bid (8mg)	12mg	1.5mg	4mg bid (8mg)
7	12mg qd (12mg)	16mg	1.5mg	12mg qd (12mg) STOP ALL OPIOIDS
8	8mg bid (16mg)	16mg	2.5mg	
9	8mg tid (24mg)	12mg	1.5mg	

- We followed Randhawa protocol until Day 7…
- Pt was d/c on Day 9 of the induction with 24mg of suboxone and hydromorphone 4mg q4 PRN to SNF.

Rational….

- Based on “occupancy theory”, maximal mu-opioid receptor binding occurs > ~ 16mg.
- Buprenorphine has higher affinity than full opioid agonist.
  - Buprenorphine exhibits 6x – 10x more affinity to MOR than naloxone (naloxone (also sufentanil) has 5x more affinity than morphine)
- Therefore, even if full opioid agonist are continued, chances are it will not be binding to mu opioid receptor as our patient’s buprenorphine dose reached 24mg on the day of discharge.
- Since mu opioid receptors are theoretically saturated with buprenorphine by this time and buprenorphine has “ceiling effect”, chances are “additional” hydromorphone patient was d/c with will not be a risk of OD.
- SNF MD understood the concept and agreed to taper off as she gets adjusted to SNF.

Herring Andrew A. Herring, Cody W. Schultz, Elaine Yang, Mark K. Greenwald, Rapid induction onto sublingual buprenorphine after opioid overdose and successful linkage to treatment for opioid use disorder, The American Journal of Emergency Medicine, Volume 37, Issue 12,2019, Pages 2259-2262, https://doi.org/10.1016/j.ajem.2019.05.053.
Blazes CK, Morrow JD. Reconsidering the Usefulness of Adding Naloxone to Buprenorphine. *Front Psychiatry*. 2020;11:549272. Published 2020 Sep 11. doi:10.3389/fpsyt.2020.549272

Overall Induction Experience

ADVANTAGES:

- Patient had NO withdrawal or precipitated withdrawal during the induction
- Patient had minimal anxiety, hence was cooperative with care
- Overall, both patient and staff were very happy with the induction process

DISADVANTAGES:

- Educating various providers
- Had to coordinate with pharmacy and nursing (need to cut the strips)
- Took 1 week (in this case, it was OK because pt didn't have places to go)
- Had to coordinate with outpatient MD (explain the concept etc…)

CLINICAL CASE COLUMN

CJA–JCA

Case Report: "Striving to Skip the Withdrawal" Using Buprenorphine–Naloxone Microdosing for Hospitalized Patients

Leslie Martin, *MD, FRCPC, MHPE*[1], Robin Lennox, *MD, CCFP*[2], Lori Regenstreif, *MD, CCFP (AM), FCFP, MScCH (AMH)*[2], Timothy O'Shea, *MD, FRCPC, MPH*[1]

- 2 case reports on patient who had concomitant treatment with full agonist opioid for pain as buprenorphine was started.
- Patient #1 was on board and was willing to taper off the use of full agonist
- Patient #2 was on board but was a bit more reluctant to come off from full agonist- very similar to our patient…!!

Table 1: Microdosing Schedule for Case 1 (AB)

	Buprenophine Dose (mg)*	HM
Day 1	0.5	2 mg IV q3h PRN = 6 mg total
Day 2	0.5	2 mg IV q3h PRN = 8 mg total
Day 3	1	2 mg IV q3h PRN = 12 mg total
Day 4	1.5	2 mg IV q3h PRN = 8 mg total
Day 5	2	2 mg IV q3h PRN = 8 mg total
Day 6	3	2 mg IV q3h PRN = 8 mg total
Day 7	4	2–4 mg PO q3h PRN = 20 mg total
Day 8	4	2–4 mg PO q3h PRN = 16 mg total
Day 9	4	2–4 mg PO q3h PRN = 12 mg total
Day 10	5	2–4 mg PO q3h PRN = 12 mg total
Day 12	6	2–4 mg PO q3h PRN = 8 mg total
Day 13	8	No HM
Day 14	10	No HM
Day 15	Discharged	

HM = hydromorphone, IV = intravenous; PO = per os.
* Dispensed as buprenorphine–naloxone.

Table 2: Microdosing Schedule for CASE 2 (CD)

	Buprenophine Dose*	HM
Day 1	0.5 mg	4 mg IV q3h
Day 2	0.5 mg	2 mg IV q2h then 4 mg
Day 3	1 mg	6 mg IV q3h
Day 4	1.5 mg	6 mg IV q3h
Day 5	2 mg	6 mg IV q3h
Day 6	3 mg	6 mg IV q3h
Day 7	4 + 2 + 2 mg	6 mg IV q3h
Day 8	4 mg BID + 2 mg	6 mg IV q3h
Day 9	4 mg TID	6 mg IV q3h
Day 10	4 mg TID	6 mg IV q3h
Day 12	8 mg BID	6 mg IV q3h
Day 14	12 mg BID	HM Contin 21 mg BID + PRN
Day 15	12 mg BID	Resumed 4 mg IV q3h
Day 16	24 mg daily	7 mg PO q3h routine
Day 17	Discharged	

HM = hydromorphone, IV = intravenous, PO = per os.
* Dispensed as buprenorphine–naloxone.

Sent home with HM and being tapered off as outpatient

Microdosing in inpatient setting….

- Many patients are hospitalized for acute infection and other complications from SUD
- Challenges unique to the inpatient: Patients are often concurrently experiencing acute pain.
- Microdosing may provide an opportunity to titrate toward a therapeutic dose of buprenorphine–naloxone before discharge, especially in patients who require “long” admission

What if patient is does NOT require long admission?

The American Journal on Addictions, 28:262–265, 2019.

ISSN: 1055-0496 print / 1521-0391 online
DOI: 10.1111/ajad.12869

Table 1 Buprenorphine dosing and use of street heroin in case 1

Day	Buprenorphine (sl)	Street heroin (sniffed)
1	0.2 mg	2.5 g
2	0.2 mg	2 g
3	0.8+2 mg	0.5 g
4	2+2.5 mg	1.5 g
5	2.5+2.5 mg	0.5 g
6	2.5+4 mg	0
7	4+4 mg	0
8	4+4 mg	0
9	8+4 mg	0

Abbreviation: sl, sublingual.

Rapid Micro-Induction of Buprenorphine/Naloxone for Opioid Use Disorder in an Inpatient Setting: A Case Series

Sukhpreet Klaire, MD, CCFP,[1] Rebecca Zivanovic, Bsc, MD,[2,3] Skye Pamela Barbic, PhD, OT,[2,4,5] Raman Sandhu, MD,[3] Nickie Mathew, MD, FRCPC,[3,6] Pouya Azar, MD, FRCPC[2,3,7]

- Achieved therapeutic dose of buprenorphine/naloxone in just 3-5 days (as compared to “Bernese protocol (can take ~ 10 days) without requiring a period of opioid withdrawal prior to initiation.
  - Bernese protocol is another microdosing protocol
- During this time, they continued to receive short-acting opioids without experiencing precipitated withdrawal symptoms.

RAPID Microdosing

Klaire S, Zivanovic R, Barbic SP, Sandhu R, Mathew N, Azar P. Rapid micro-induction of buprenorphine/naloxone for opioid use disorder in an inpatient setting: A case series. The American journal on addictions. 2019;28(4):262-265. doi:10.1111/ajad.12869

Hydromorphone continued!

TABLE 1. Titration schedule for Case 1

	Buprenorphine/Naloxone*		Hydromorphone	
	Dosing	Total Daily Dose	Dosing	Total Daily Dose
Day 0	N/A		1-4 mg IV q4h PRN	3 mg
Day 1	0.25g SL q4h	1 mg	1-4 mg IV q4h PRN	11 mg
Day 2	0.5 mg SL q4h	2.5 mg	1-4 mg IV q4h PRN	15 mg
Day 3	1 mg SL q4h	5 mg	1-4 mg IV q4h PRN	15 mg
Day 4	2 mg SL q4h	8 mg	1-4 mg IV q4h PRN	4 mg
Day 5	16 mg SL daily	16 mg	Discontinued	

*Expressed as milligrams of buprenorphine in buprenorphine/naloxone sublingual tablet.

TABLE 2. Titration schedule for Case 2

	Buprenorphine/Naloxone*		Hydromorphone	
	Dosing	Total Daily Dose	Dosing	Total Daily Dose
Day 0	N/A		3 mg PO q4h regular 2-4 mg PO q4h PRN	24 mg
Day 1	0.5 mg SL q3h	2.5 mg	3 mg PO q4h regular 2-4 mg PO q4h PRN	26 mg
Day 2	1 mg SL q3h	8 mg	3 mg PO q4h regular 2-4 mg PO q4h PRN	24 mg
Day 3	12 mg SL daily	12 mg	Discontinued	

*Expressed as milligrams of buprenorphine in buprenorphine/naloxone sublingual tablet.

The American Journal on Addictions, 28:262–265, 2019.

ISSN: 1055-0496 print / 1521-0391 online
DOI: 10.1111/ajad.12869

Rapid Micro-Induction of Buprenorphine/Naloxone for Opioid Use Disorder in an Inpatient Setting: A Case Series

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Conclusion:

- Rapid micro-induction may be useful for an inpatient setting where discharges are generally not delayed to complete buprenorphine/naloxone induction.
  - May increase the number of patients leaving hospital on a therapeutic dose
- Simplify the induction process (no holding opioids, assessing withdrawal).
- May also be applicable in patients with pain who are receiving prescribed opioids.
- Maybe safer for OUD patients in general: buprenorphine/naloxone carries a better safety profile than other opioids.

Klaire S, Zivanovic R, Barbic SP, Sandhu R, Mathew N, Azar P. Rapid micro-induction of buprenorphine/naloxone for opioid use disorder in an inpatient setting: A case series. The American journal on addictions. 2019;28(4):262-265. doi:10.1111/ajad.12869

MACRODOSING

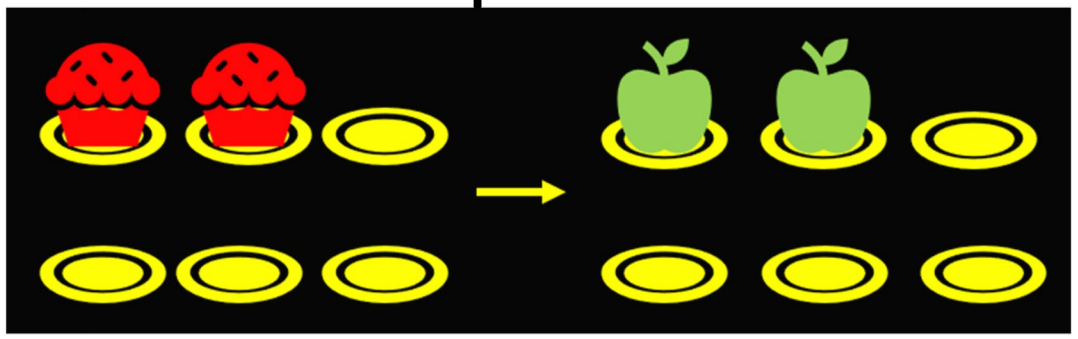
MACRODOSING in inpatient setting:

Monteiro C, Golden R. ASAM Poster. Buprenorphine macro-dosing induction for OUD in the inpatient setting: a case series.

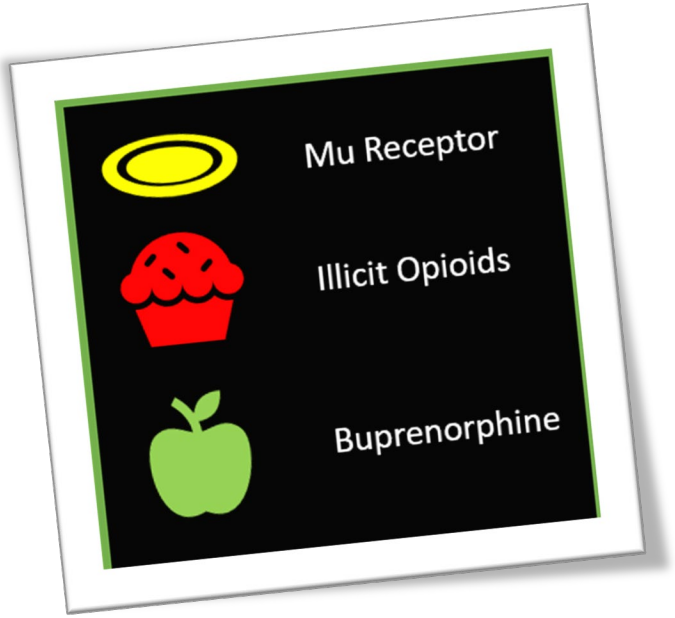
- 15 cases, COWS > 8, at least >4 hours since the last full agonist administration
- 14 patients got 16mg, 1 patient got 20mg
- NONE had precipitated withdrawal
- 10/15 patients had complete resolution of opioid withdrawal
- 5/15 patients had persistent withdrawal
  - 2 improved with additional 8 mg (was using fentanyl) – total 24mg
  - The remaining 3 patients had persistent withdrawal despite total doses of 32-40 mg on induction. 2/3 were using fentanyl.
- 4/15 patients receiving full opioid agonist therapy for pain during hospitalization and mild withdrawal symptoms. **ALL had successful induction** with 16 mg 4-6 hours after last full opioid agonist administration.
- **Conclusions**: Our findings support the theory that macro-dosing induction stimulates sufficient opioid receptors to avoid precipitated withdrawal and ameliorate existing withdrawal. The role of concurrent fentanyl use needs to be further explored.
- Similar concept with treating “precipitated withdrawal” – just treating from the beginning

Rational: Similar to treating precipitated withdrawal

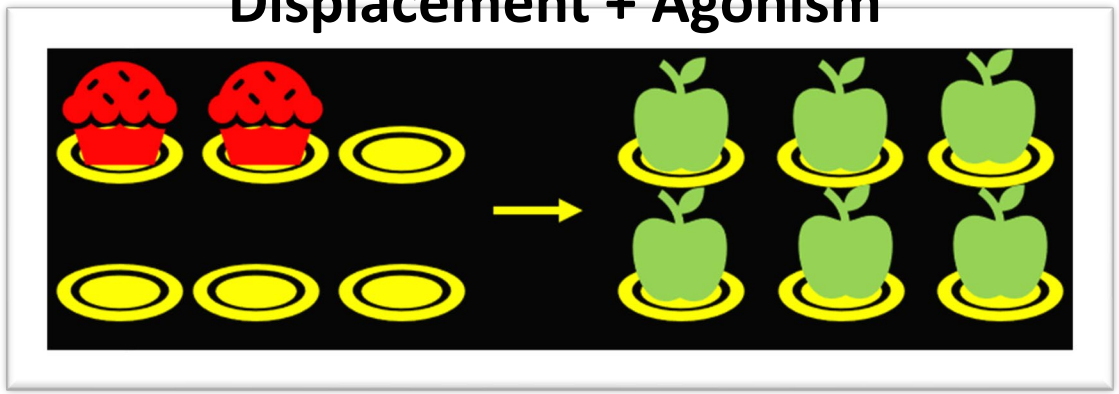
Displacement



→ **Precipitated Withdrawal**



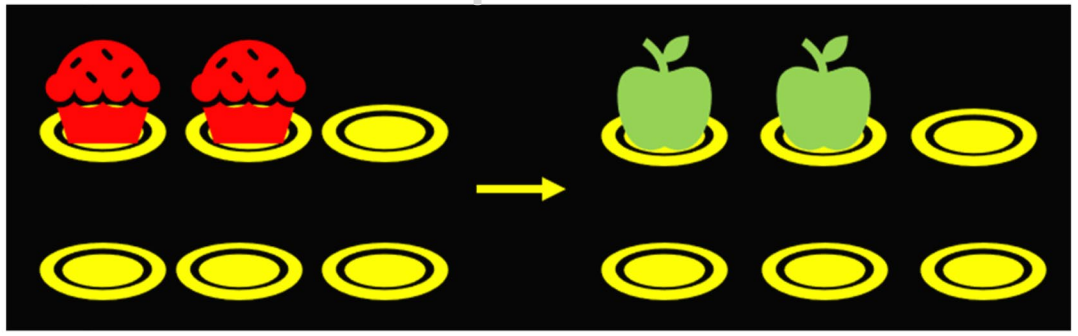
Displacement + Agonism



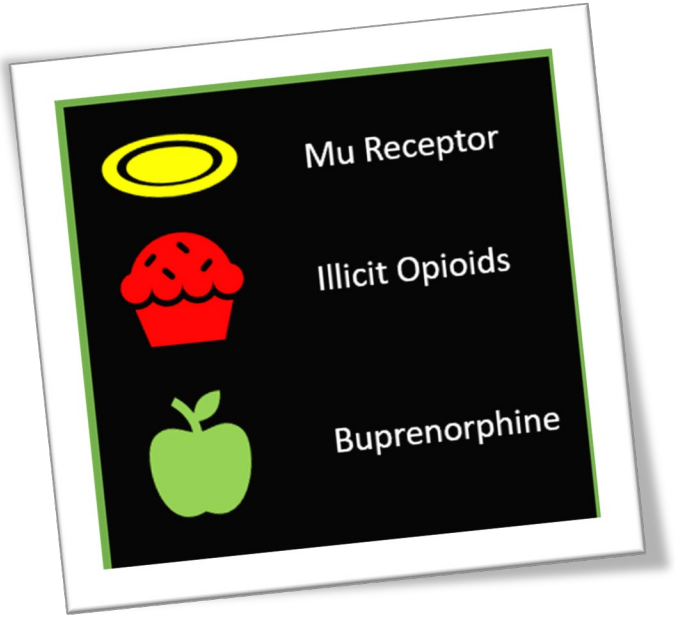
→ **Relief**

Rational: Similar to treating precipitated withdrawal

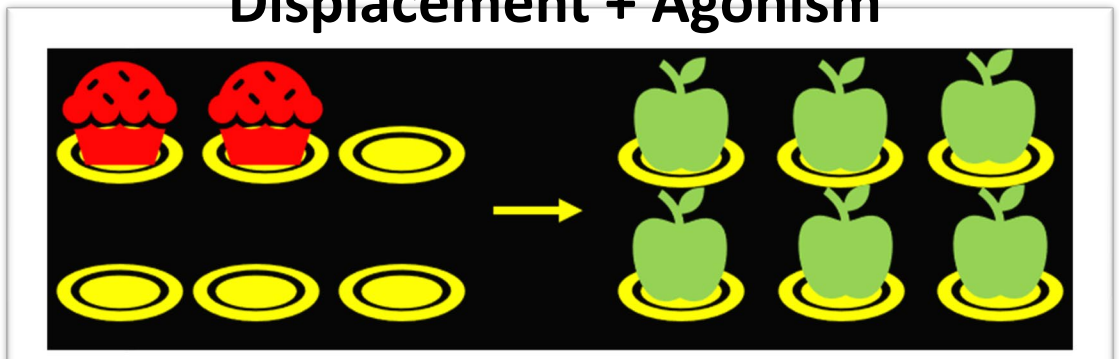
Displacement



→ Precipitated Withdrawal



Displacement + Agonism



→ **MACRODOSING!**

Potential MACRODOSING protocol (inpatient):

- Day #1: Buprenorphine 8mg SL for COWS of at least 5
- 1 hour later:
  - If **mild improvement**: give Buprenorphine 8mg SL
  - If **significant improvement**: give Buprenorphine 8mg SL **8 hours after** initial dose if significant improvement
  - If **withdrawal worsen:** give Buprenorphine 16mg SL
- Maximum dose of 32mg/day?
- https://sites.rutgers.edu/mat-coe/wp-content/uploads/sites/473/2021/06/06.04-ECHO_FINAL-1.pdf

Sample MACRODOSING protocol (home):

- Day 1: Take 8mg with COWS 8-10
  - If worse (precipitated withdrawal): advise to take 4-8mg q1 until additional buprenorphine hourly until symptoms resolve (higher doses for greater symptoms of withdrawal)
  - Otherwise, 4mg q2 hours PRN for a maximum dose of 24mg on day 1
- Day 2, take the total daily dose of day 1 and may divide the dose.
  - Patient may take up to a maximum dose of 24mg on day 2.
- Steady state may take faster than 5-7 days
- https://sites.rutgers.edu/mat-coe/wp-content/uploads/sites/473/2021/06/06.04-ECHO_FINAL-1.pdf

Macrodosing - Conclusion

ADVANTAGES

- Possible reduction of anxiety due to faster induction process
- Greater receptor saturation may reduce risk of precipitated withdrawal
- Appeared safe
- Can utilize i.e. in ED or shorter inpatient stay
- Reduce return of withdrawal symptoms
- May reduce immediate OD after discharge

DISADVANTAGES

- No definite evidence yet - Current literature only available in case series
- Risks unclear with:
  - Pregnancy (i.e. safety)
  - Concomitant alcohol/BZD use (mixed substance OD has been reported with bup)
  - Switching from methadone

Conclusion

- There is a higher risk of precipitated opioid withdrawal in those who uses illicit drug due to contamination with fentanyl
- Precipiated opioid withdrawal can be treated with high dose of buprenorphine
- There are other induction methods available now to minimized the risk of precipitated opioid withdrawal as well as allowing opioids to be continued
- These induction methods are however still based on case reports and case consensus alone, but may be beneficial in certain types of patients when traditional induction doesn’t work.