AETC AIDS Education & Training Center Program Mountain West

BUPRENORPHINE FOR OPIOID USE DISORDER

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Disclosures

NO CONFLICTS OF INTEREST OR RELATIONSHIPS TO DISCLOSE.

DATA CONSIDERATIONS

Data in this presentation offer a limited perspective of how systemic, social, and economic factors impact health. We recognize that racism, not race, creates and perpetuates health disparities.

To Learn More:
https://www.cdc.gov/minorityhealth/racism-disparities

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Acknowledgment

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AETC AIDS Education & Training Center Program
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LEARNING OBJECTIVES

1. To identify the types of medications for opioid use disorder (OUD), with focus on buprenorphine.
2. To describe approaches to counseling patients on MOUD options.
3. To outline practical considerations for buprenorphine initiation for OUD.

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SUBSTANCE USE DISORDERS AND HIV

- Addressing substance use disorder in people with HIV is important for several reasons.
- Substance use can:
  - Drive transmission of HIV infection (e.g. injection drug use)
  - Increase high-risk sexual behaviors
  - Reduce HIV treatment adherence
  - Worsen neurologic and other complications of HIV infection
  - Increase viral load, further disease progression, and increase mortality in people with HIV even if on ART regimen (Dash 2015)
- Treating SUD can:
  - Reduce risk of HIV acquisition and transmission
  - Improve HIV and other medical treatment adherence

Dash 2015

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King County Fatal Overdose Dashboard

Source: King County Medical Examiner's Office

As of **5/10/2023**

Public Health
Seattle & King County

2023 Summary

Confirmed Drug Overdose or Alcohol Poisoning	435
Possible (unconfirmed) Overdose	5
Probable (unconfirmed) Overdose	58

# of Overdose Deaths YTD in 2023 that Involved:

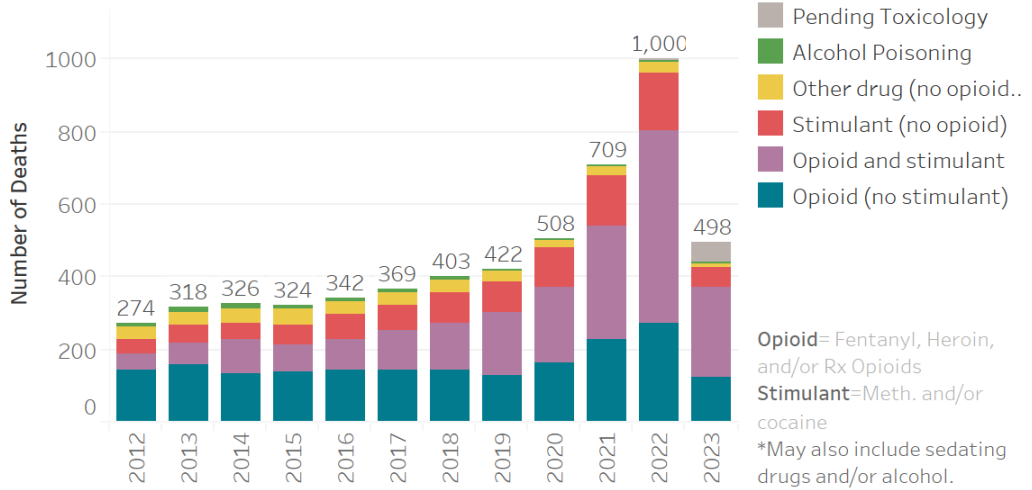
Opioids	372	Fentanyl	359	Methamphetamine	235

# of Overdose Deaths in 2022 that Involved:

Opioids	802	Fentanyl	712	Methamphetamine	528

Drug & Alcohol Poisoning Deaths, King County

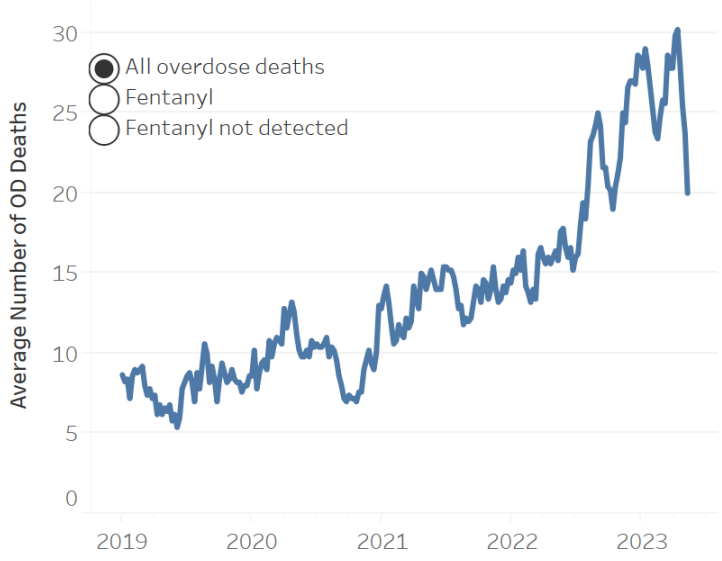
(Note: Bar chart can be viewed in terms of counts or rates; each decedent with an overdose death is represented once.)



Opioid= Fentanyl, Heroin, and/or Rx Opioids
Stimulant=Meth. and/or cocaine
*May also include sedating drugs and/or alcohol.

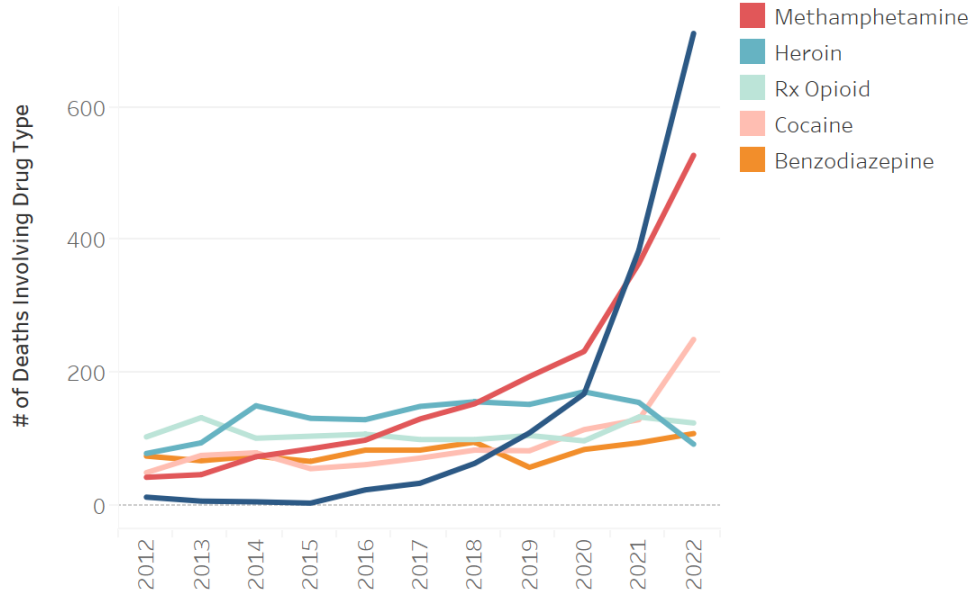
Fentanyl Overdose Trends

Switch data view: Overdose deaths by week (rolling average)



Drugs Involved in Confirmed Overdose Deaths

(Note: A decedent may be represented in multiple lines)



Fentanyl pressed pills ("blues")

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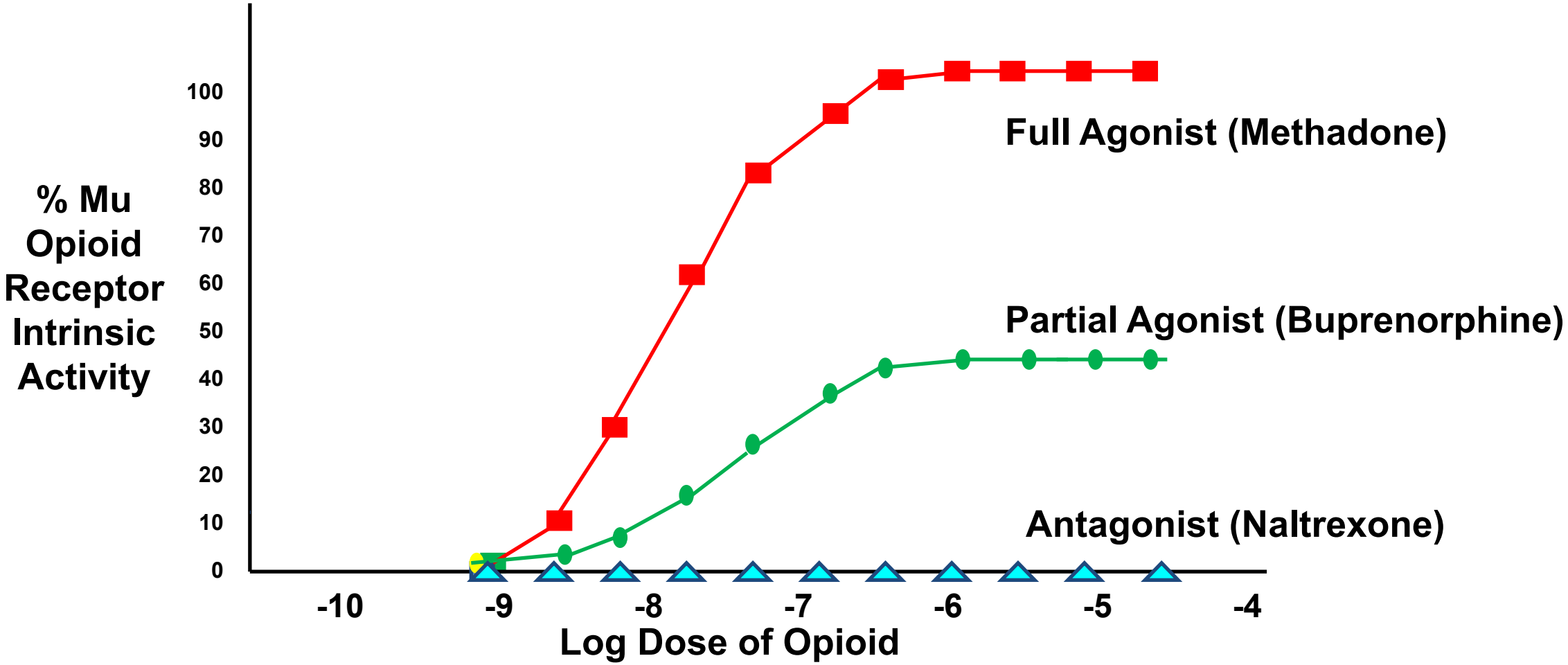
FDA APPROVED MEDICATIONS FOR OUD (MOUD)



From Jonathan Buchholz, MD

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METHADONE

- Full agonist at mu opioid receptor (MOR)
- Peak level in 4 hours
- Half life of mean 24 hours, wide range 8-59 hours
- Usual maintenance dose: 80-120 mg daily

SAMHSA TIP 63: “Medications for Opioid Use Disorder” 2021

BUPRENORPHINE

- Partial agonist at MOR
- Ceiling effect on respiratory depression (lower risk of overdose)
- High affinity for MOR (displaces other opioids)
- Poor oral bioavailability; given sublingually or subcutaneously for OUD (transdermal or buccal for pain)
- Sublingual:
  - Peak level 3-6 hours
  - 24-48 hour duration
  - Half life >24 hours
  - Typical maintenance dose: 16-24 mg daily (typical maximum 32 mg daily)

SAMHSA TIP 63: “Medications for Opioid Use Disorder” 2021

NALTREXONE

- Opioid antagonist
- Monthly IM (preferred) or daily PO formulations
- High dropout rates in study; for those who were adherent to treatment, naltrexone more effective than placebo in maintaining abstinence
- Up sides
  - Good for those who want to be opioid free
  - IM formulation is less burdensome than daily dosing
- Down sides
  - Requires detoxification before initiation or severe withdrawal will be precipitated
  - Unclear mortality benefit in comparison to buprenorphine or methadone

ACCESS TO OUD CARE

Factor	Methadone	Buprenorphine
Treatment Setting	Opioid Treatment Program (OTP)	Office-Based Opioid Treatment (OBOT) Program (within general medical practice)
Provider	OTP provider only (for OUD)	All clinicians with current DEA registration including Schedule III authority (X-waiver NO LONGER required as of 1/12/2023!)
Pharmacy	Dispensed by OTP clinic only	Non-OTP pharmacy ok
Take-Home Doses	Per OTP policy. (Up to 28 days if stable per SAMHSA)	Does not require observed dosing.

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A NOTE ON BUPRENORPHINE PRESCRIBING…

- Buprenorphine for OUD can now be prescribed by anyone with DEA registration including Schedule III authority as of 1/12/2023. **No X-waiver needed!**
- After 6/27/2023, for new or renewing DEA registrations, a **one-time requirement of 8 hours of training on substance use disorders (SUDs)** is now required
- If you previously got your X-waiver, this counts!

SAMHSA
https://www.samhsa.gov/medications-substance-use-disorders/removal-data-waiver-requirement
https://www.deadiversion.usdoj.gov/pubs/docs/MATE_Training_Letter_Final.pdf

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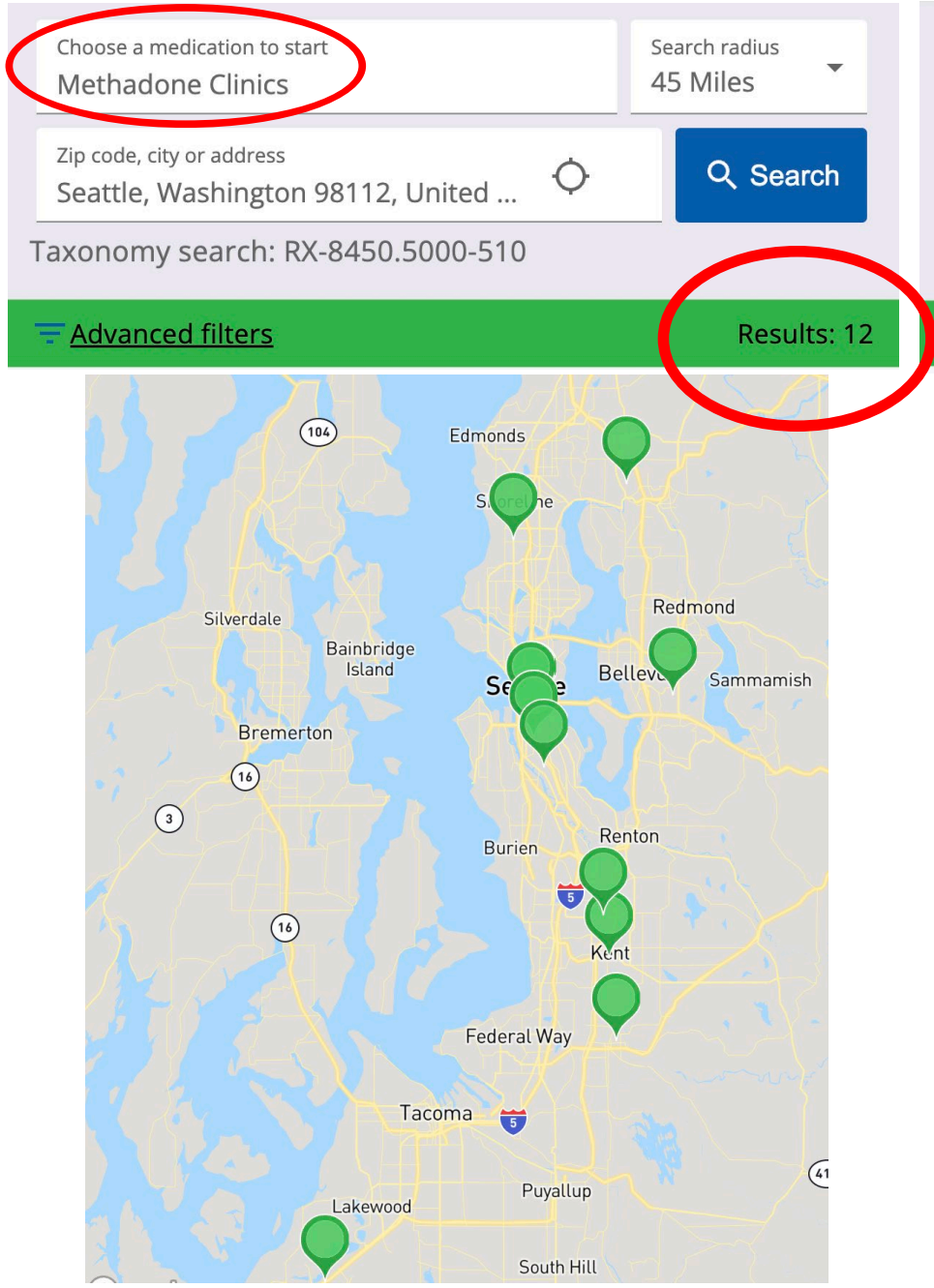

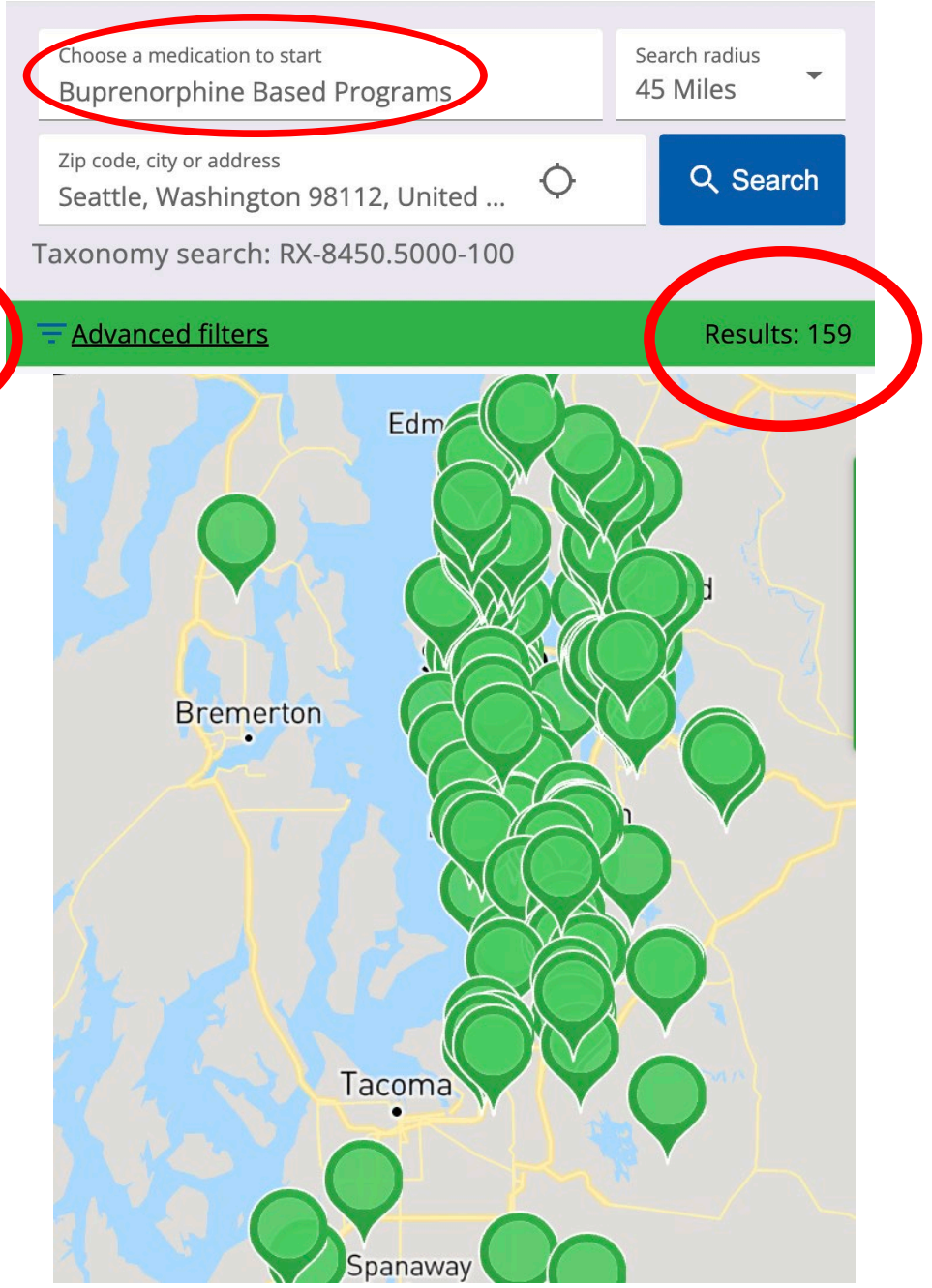

WA Recovery Helpline MOUD Locator, https://search.warecoveryhelpline.org/

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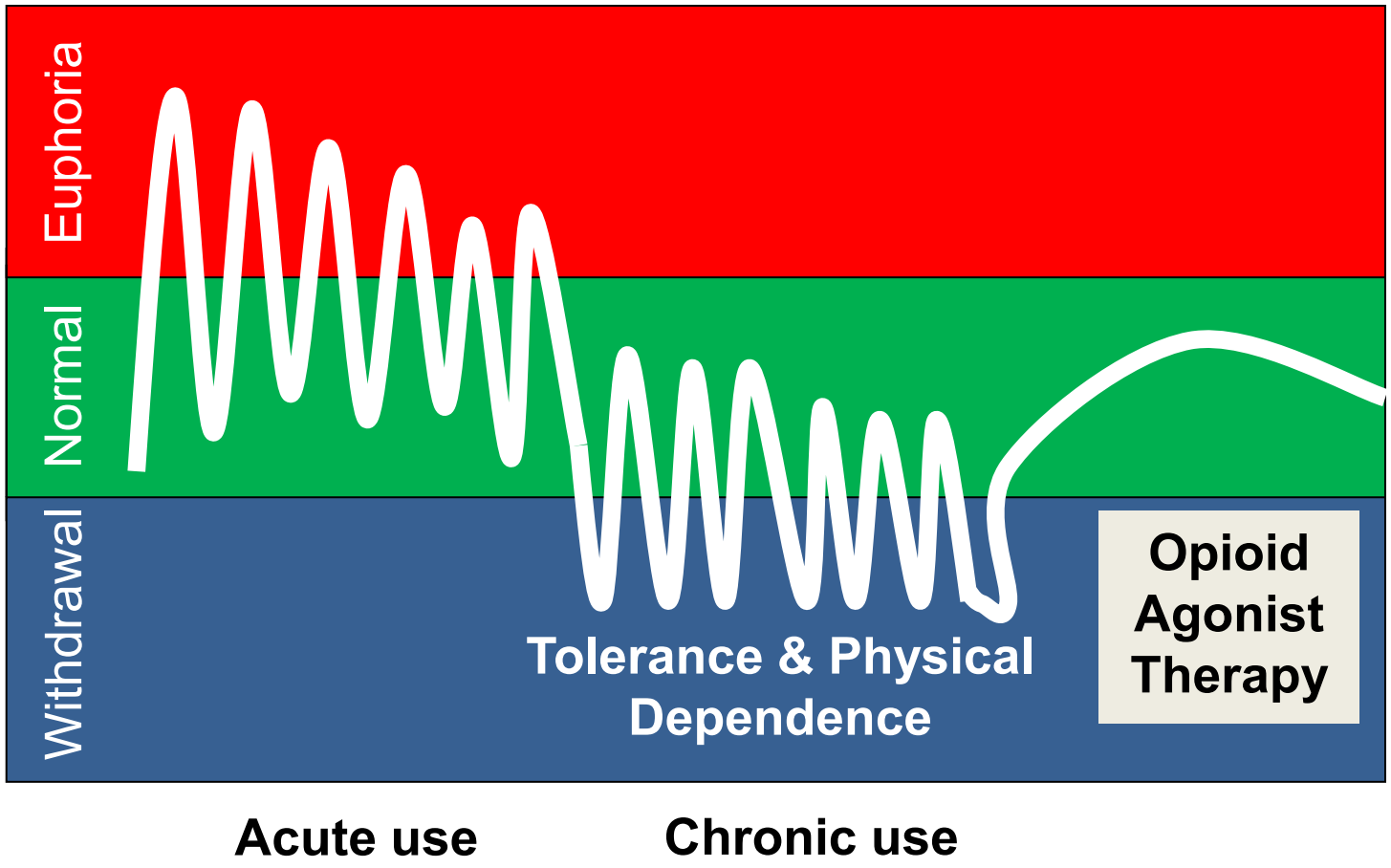
COUNSELING ON OUD TREATMENT

- Discuss main key components of treatment
  - Medications for opioid use disorder (MOUD)
  - Psychosocial interventions (e.g. counseling, mutual support groups)
- First-line treatment for OUD is medications, with adjunctive psychosocial interventions
- Shared decision making is key!
- Decreased mortality is associated with opioid agonist treatment (buprenorphine or methadone)

Larochelle 2018

AREN'T YOU JUST REPLACING ONE DRUG FOR ANOTHER?



On therapeutic doses of opioid agonist therapy, patients should have reduced withdrawal symptoms and opioid cravings, and do not "get high."

Opioid agonist therapy helps restore balance/stability in mu opioid receptor activity to support recovery.

Adapted from Jonathan Buchholz, MD

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POSSIBLE REASONS TO CHOOSE BUPRENORPHINE

- Desire to avoid treatment in OTP setting
  - Structured setting
  - Location
  - Need for observed dosing and dispensing at OTP
- Desire to receive care in integrated care setting (e.g. from PCP/OBOT program)
- Methadone side effects or drug-drug interactions
- Dosing schedule and route of administration
  - e.g. Buprenorphine XR injectable form
- Preparation for transition to opioid antagonist treatment (naltrexone)
- **Patient-driven (rather than provider-driven) transitions to buprenorphine are associated with higher rate of success!** (Bhatraju 2022)

Bhatraju 2022

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LIMITATIONS OF BUPRENORPHINE

- Difficulty with tolerating opioid withdrawal
- Risk of return to use when opioid agonist dose is tapered
  - For example, in methadone to buprenorphine transitions
- Precipitated withdrawal if buprenorphine given too soon after stopping opioid agonist
- Inability to quickly achieve therapeutic effect with buprenorphine

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BUPRENORPHINE INITIATION PROTOCOLS

- Standard initiation
- High-dose initiation
- Low-dose initiation
- Practical considerations

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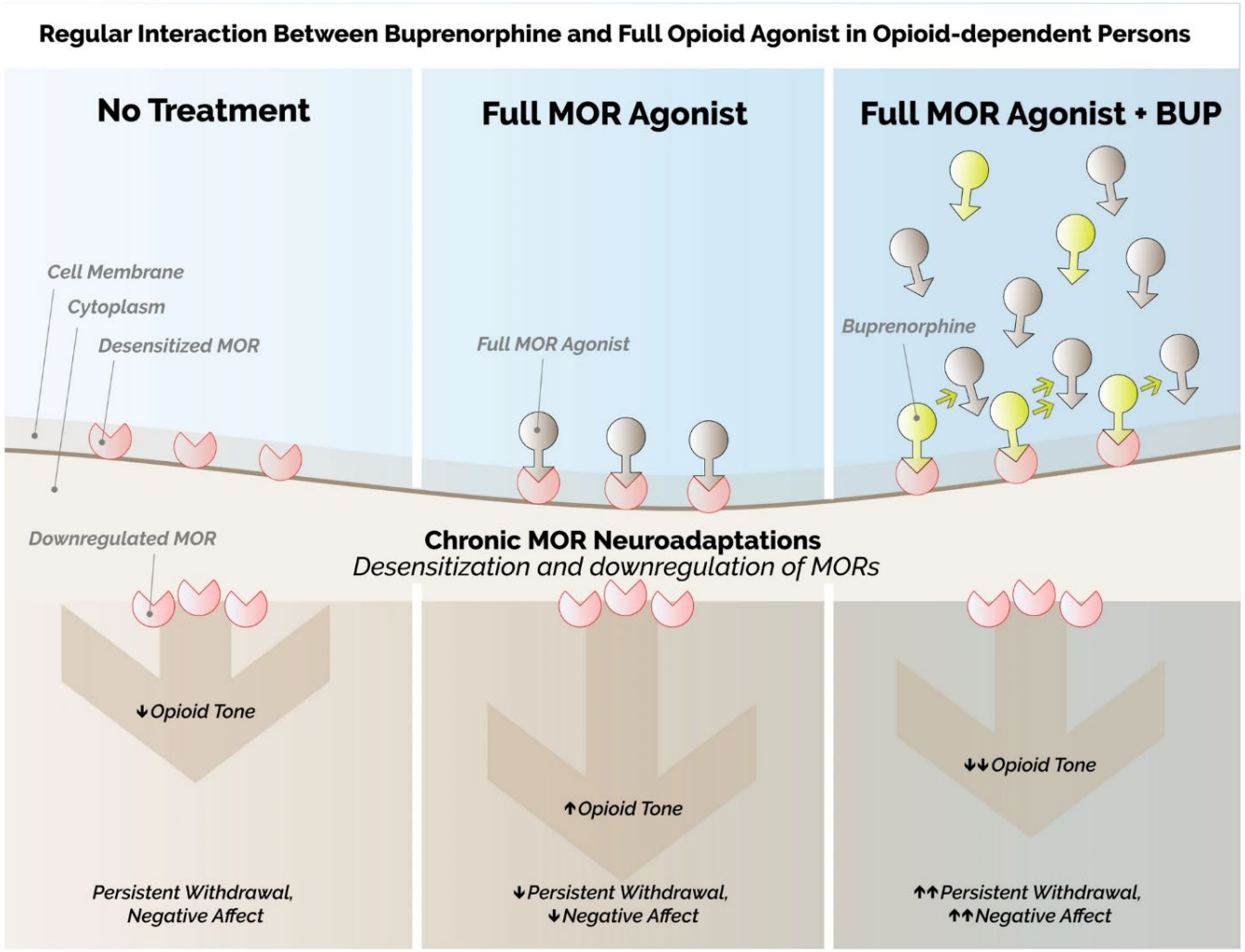
BUPRENORPHINE COMPETITIVELY BINDS TO MU OPIOID RECEPTOR (MOR)



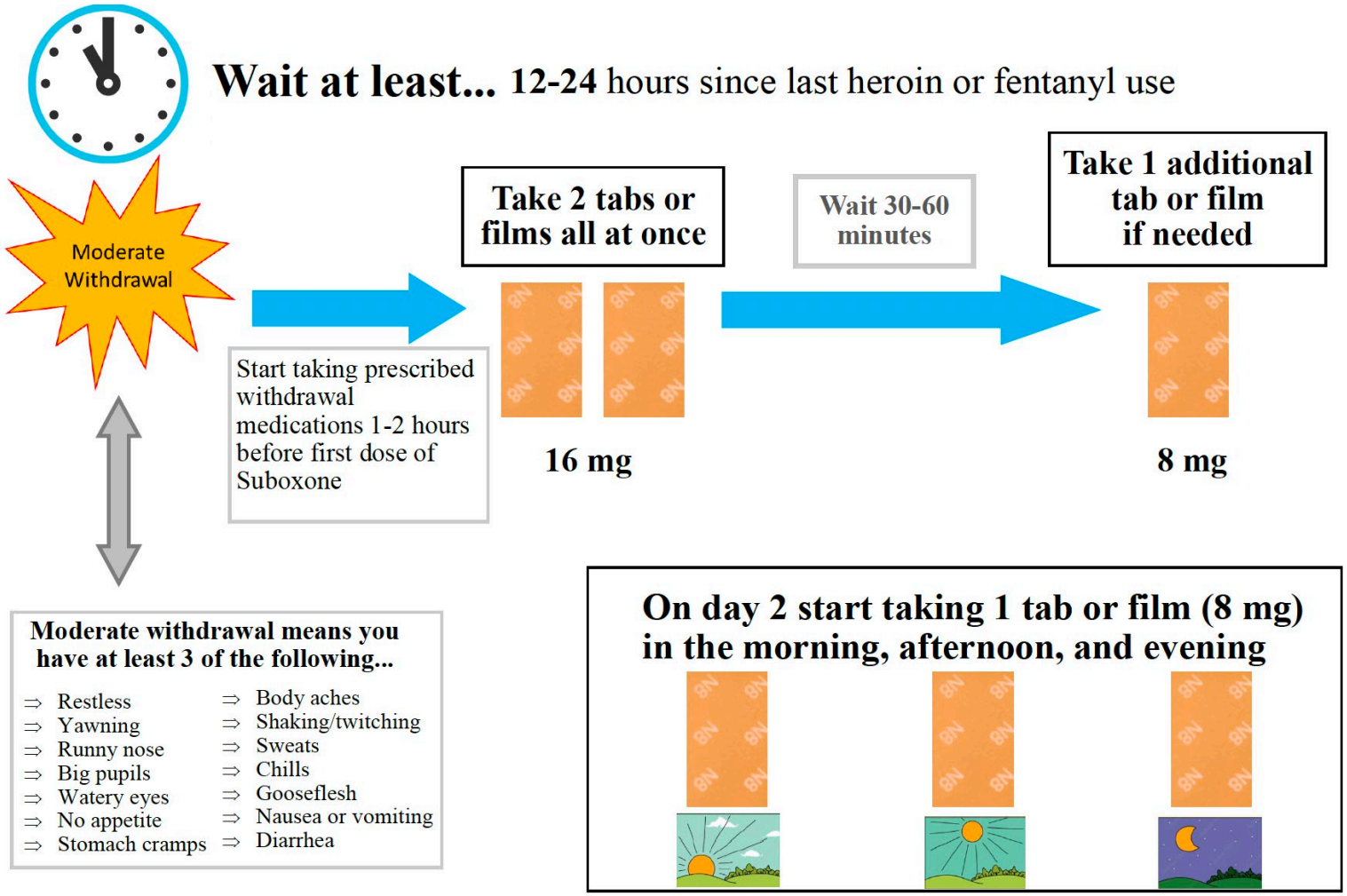
De Aquino 2021

STANDARD BUPRENORPHINE INITIATION

- Stop opioids and wait until patient is in opioid withdrawal (COWS>10 typically), usually after:
  - Short-acting opioids (heroin, hydrocodone, oxycodone): 12-16 hr
  - Intermediate-acting opioids (e.g. oxycodone ER): 17-24 hr
  - Long-acting opioids (e.g. methadone, fentanyl): 36+ hours
- Buprenorphine-naloxone started, uptitrated until withdrawal resolves (usually 1-3 days)
- Typically no more than 8-16 mg bup total on day 1
- Pro: less complex protocol
- Cons:
  - Risk for return to use after stopping opioids
  - May take days to achieve therapeutic buprenorphine level

HIGH-DOSE INITIATION

Like conventional initiation, but higher buprenorphine dose on day 1 (16-32 mg)



From David Sapienza, MD

HIGH-DOSE INITIATION PROTOCOL

- Like conventional initiation, but higher buprenorphine dose on day 1 (16-32 mg)
- Advantages
  - Less complex protocol than low- or standard-dose start
  - Could be more effective in achieving therapeutic dose while minimizing withdrawal period
- Limited evidence in literature (for now)
  - Herring 2021: retrospective case series, ER setting, up to 32 mg max compared to standard initiation (up to 12 mg), no precipitated withdrawal or other adverse events noted associated with bup high-dose start
  - Snyder 2023: retrospective cohort study, ER setting, 9.5% of patients used fentanyl. Rare precipitated withdrawal (1.6%, or 8/492 patients). Of those with fentanyl use, 2 cases (4.5%) of precipitated withdrawal

Herring 2021, Snyder 2023

LOW-DOSE BUPRENORPHINE INITIATION

- Aka the “Bernese Method”
- Start buprenorphine at low doses while continuing full agonist (i.e. methadone)
- Intention is to minimize precipitated withdrawal
- Pros:
  - May be more acceptable if negative prior experiences with standard buprenorphine initiation
  - Minimizes withdrawal symptoms
- Cons:
  - More complex instructions
  - Limited evidence in outpatient setting

Hämmig 2016

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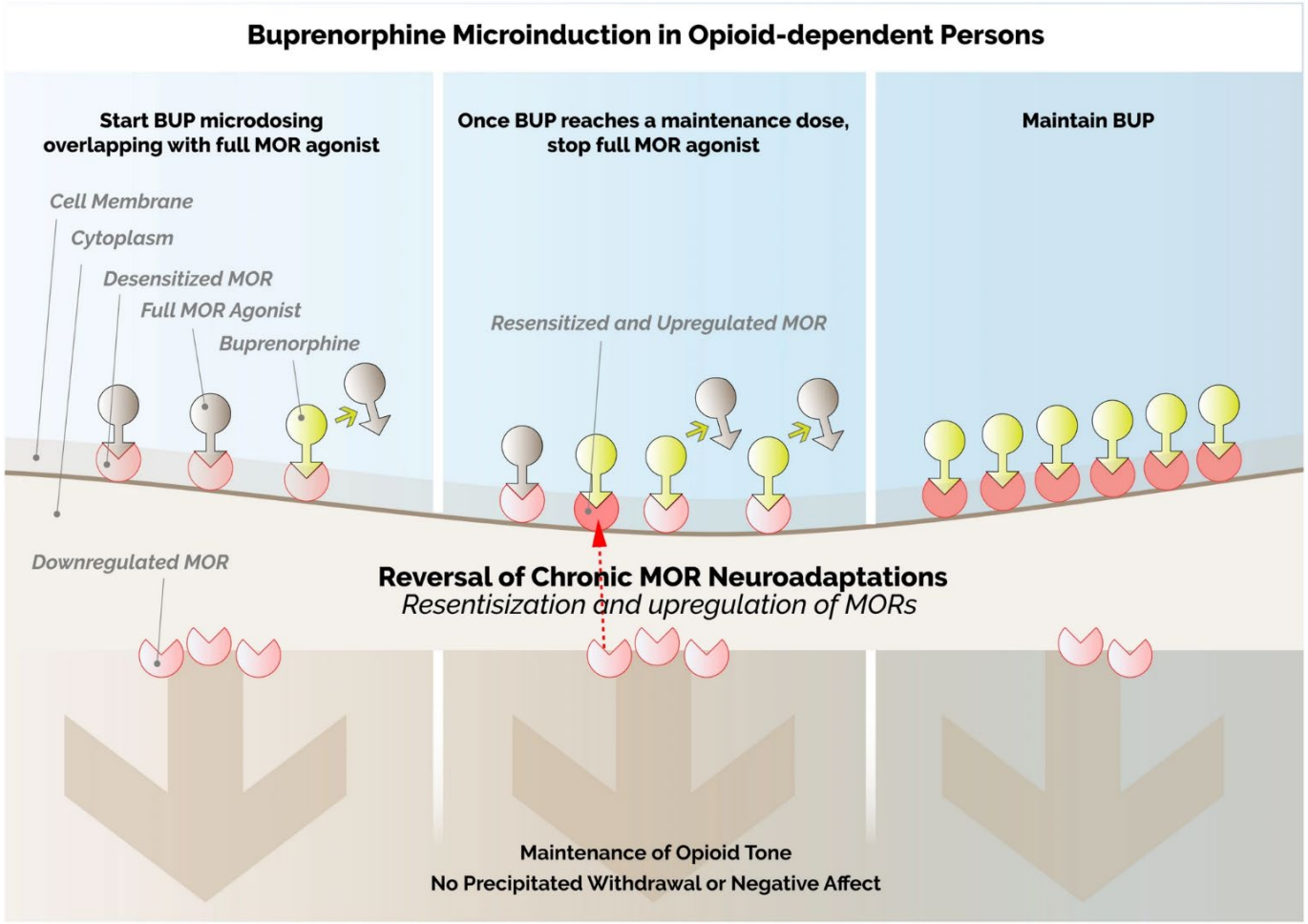
LOW-DOSE BUPRENORPHINE INITIATION: THE "BERNESE METHOD"

- Proposed that small doses of buprenorphine should not precipitate opioid withdrawal
- Buprenorphine has high affinity and long binding time at the mu opioid receptor
- Buprenorphine will gradually displace full opioid agonists and accumulate at opioid receptor
- Original study: n=2

Hämmig 2016

LOW DOSES OF BUPRENORPHINE AVOID SIGNIFICANT WITHDRAWAL



De Aquino 2021

ORIGINAL RESEARCH

Low Dose Buprenorphine Induction With Full Agonist Overlap in Hospitalized Patients With Opioid Use Disorder: A Retrospective Cohort Study

Bhatraju, Elenore P. MD, MPH; Klein, Jared W. MD, MPH; Hall, Allana N.; Chen, David R. MD; Iles-Shih, Matthew MD, MPH; Tsui, Judith I. MD, MPH; Merrill, Joseph O. MD, MPH

Author Information

Journal of Addiction Medicine 16(4):p 461-465, 7/8 2022. | ***DOI:*** 10.1097/ADM.0000000000000947

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LOW-DOSE BUPRENORPHINE IN THE HOSPITAL: BHATRAJU 2022

- Retrospective cohort study, n=62, hospitalized patients at Harborview Medical Center
- 42 (68%) patients on methadone at time of bup initiation
  - 14 patients on methadone prior to admission
  - 28 started on methadone during admission
- 79% (33/42) of those on methadone successfully transitioned to buprenorphine
- Unsuccessful transition significantly associated with:
  - Older age
  - Reporting any withdrawal symptoms during transition
  - Switching to buprenorphine for post-hospital placement

Bhatraju 2022

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TABLE 1. Microdose with Overlap Protocol

	Dose of Buprenorphine*	Full Agonist
Day 1	0.5 mg once	Baseline dose
Day 2	0.5 mg BID	Baseline dose
Day 3	1 mg BID	Baseline dose
Day 4	2 mg BID	Baseline dose
Day 5	4 mg BID	Baseline dose
Day 6	8 mg Once	Baseline dose
Day 7*	8 mg AM/4 mg PM	Baseline dose
Day 8	8 mg BID	None

*Buprenorphine/naloxone films or tablets were utilized. Buprenorphine specific doses are reported here for simplicity.

Bhatraju 2022

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ORIGINAL RESEARCH

Low-dose Buprenorphine Initiation in Hospitalized Adults With Opioid Use Disorder: A Retrospective Cohort Analysis

Dana Button, BS, Jennifer Hartley, MD, PhD, Jonathan Robbins, MD, MS, Ximena A. Levander, MD, MCR, Natashia J. Smith, BS, and Honora Englander, MD

(*J Addict Med* 2022;16: e105–e111)

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LOW-DOSE BUPRENORPHINE IN THE HOSPITAL: BUTTON 2022

TABLE 2. Characteristics of Low-dose Buprenorphine Initiations

Induction Characteristic	n (%)
Unique low-dose initiation	72
Reason for low-dose initiation[*]	
Co-occurring pain	66 (91.7)
Anxiety around thought of withdrawal	50 (69.4)
Transition from high dose methadone	21 (29.2)
History of precipitated withdrawal	7 (9.7)
Opioid withdrawal intolerance	5 (6.9)
Other	13 (18.1)
Days of low-dose initiation in hospital – mean (SD)	6 (2.7)
Low-dose initiation completion status	
Completed in hospital	50 (69.4)
Scheduled to complete as outpatient	9 (12.5)
Discontinued in hospital[†]	13 (18.1)
Premature discharge during low-dose initiation	2 (2.8)

[*]Not mutually exclusive.

†One individual did not complete two low-dose initiations before the third, completed low-dose initiation.

- Retrospective cohort study, n=68, hospitalized patients at OHSU Medical Center seen by addiction consult service
- Mean prescribed MME before low-dose initiation: 198 (SD 98). (approximately methadone 25 mg dose)
- 29.2% (n=21) of patients on “high dose” methadone (not specified, but >80 mg daily dose?)

Button 2022

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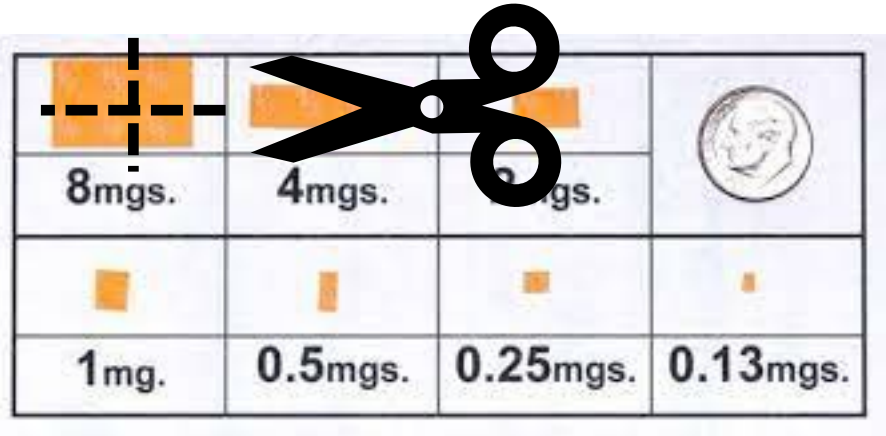
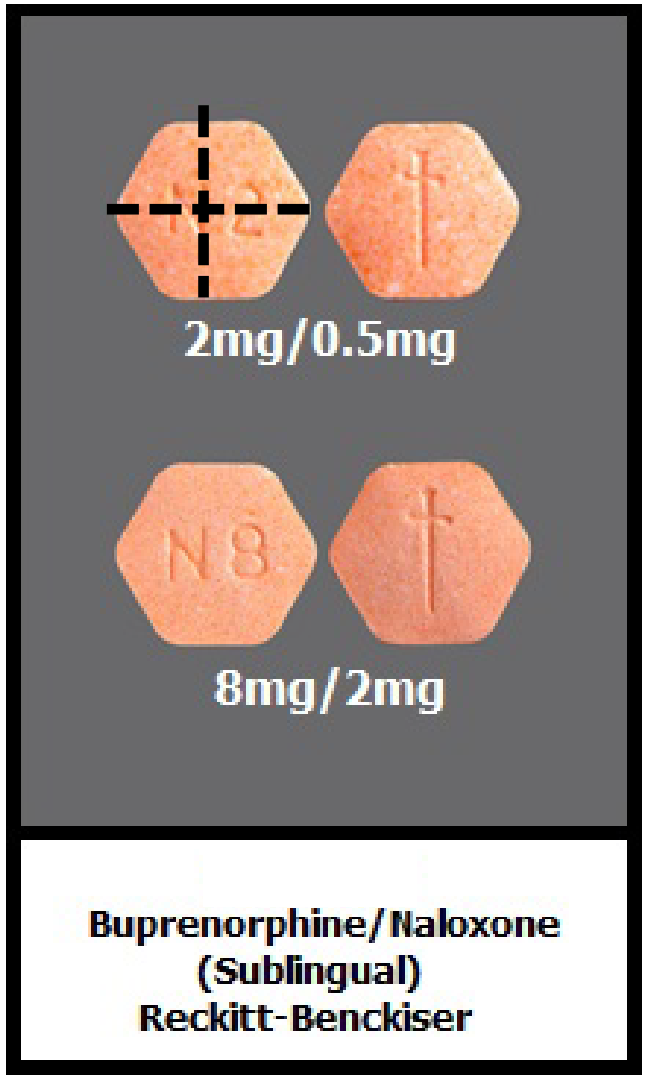
OUTPATIENT LOW-DOSE INITIATION EXAMPLE: ETS

Day	Date	Actual Dose/Day	Film or SL tablets	Methadone Dose
Buprenorphine/Naloxone Film 2mg/0.5mg				
Day 1		0.5mg	¼ film once daily	Continue current dose
	See ETS Medical Provider on Day 1			
Day 2		0.5mg once daily	¼ film once daily	Continue current dose
Day 3		1mg once daily	½ film once daily	Continue current dose
Day 4		1mg once daily	½ film once daily	Continue current dose
Begin Buprenorphone/Naloxone Tablets for remainder of transition				
Day 5		2mg once daily	1 x 2mg/0.5mg daily	Continue current dose
Day 6		2mg once daily	1 x 2mg/0.5mg daily	Continue current dose
Day 7		4mg once daily	2 x 2mg/0.5mg daily	Meet with your ETS medical provider to discuss when to reduce or discontinue methadone dose.
	See ETS Medical Provider on Day 7			
Day 8		4mg once daily	2 x 2mg/0.5mg daily	
Day 9		6mg once daily	3 x 2mg/0.5mg daily	
Day 10		6mg once daily	3 x 2mg/0.5mg daily	
Day 11		8mg once daily	1 x 8mg/2mg daily	
Day 12		8mg once daily	1 x 8mg/2mg daily	
Day 13		12mg once daily	2 x 2mg/0.5mg along with 1 x 8mg/2mg daily	
Day 14		16mg once daily	2 x 8mg/2mg daily	Return to ETS
	See ETS Medical Provider on Day 14			

BUPRENORPHINE FILMS AND TABLETS

¼th of a 2/0.5 mg bup-nal film or tab = 0.5 mg buprenorphine





COMPARISONS OF PROTOCOLS

- Most studies are observational case series with heterogeneous populations, methods, and reported outcomes
- Low-dose initiation has more evidence for efficacy
- Most data of low-dose initiation is from inpatient setting; limited generalizability to outpatient setting
- Limited data on high-dose transition from methadone to buprenorphine, but anecdotally some potential benefits to this strategy

PRACTICAL CONSIDERATIONS

- Practice setting to guide buprenorphine initiation? (OTP, OBOT?)
- Inpatient versus outpatient initiation?
- Symptomatic medications
- Advice for patients

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OBOT-BASED BUPRENORPHINE INITIATION: PRACTICAL APPROACH

- Prescribe buprenorphine-naloxone and PRN comfort medications with instructions on home initiation
- Schedule provider visits starting on day 1 of initiation protocol, at least weekly and PRN
- Follow-up via telephone as needed (with RN or other clinic staff)
- If transitioning from methadone to buprenorphine, should collaborate with OTP provider (have ROI signed to allow for communication with OTP)

INPATIENT BUPRENORPHINE INITIATION

- Could consider inpatient admission for withdrawal management and initiation onto buprenorphine, if available
- Can more closely monitor patient
- Provider/RN can manage complicated dosing schedule
- Can adjust protocol more quickly in response to clinical status

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ADJUNCTIVE MEDICATIONS FOR OPIOID WITHDRAWAL

Symptom	Medication	Typical Dose Range
Anxiety, restlessness, insomnia	Clonidine	0.1-0.2 mg q2H PRN, NTE 1.2 mg daily (avoid if hypotensive), taper by 0.1-0.2 daily
	Gabapentin	300 mg TID PRN
	Hydroxyzine	25-50 mg q6H PRN
Muscle spasms	Methocarbamol	500 mg TID PRN
Muscle aches, joint pain, headache	Ibuprofen	400-800 q6H PRN
	Acetaminophen	500-1000 mg q6H PRN
Nausea, vomiting	Ondansetron	4-8 mg q8H PRN
Abdominal cramping	Dicyclomine	20 mg 4x daily PRN
Diarrhea	Loperamide	2 mg 4x daily PRN

Srivastava 2020

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OTHER PRACTICAL CONSIDERATIONS

- Advise patient to consider reducing work, other obligations as able during initiation (likely 1-2 weeks)
- Ensure clinical support (e.g. access to clinic RN via telephone) available for patient PRN during initiation

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BUPRENORPHINE INITIATION: SUMMARY

- The decision on MOUD depends on various factors
  - **Patient preferences**
  - Risk-benefit discussion
  - Adherence considerations
  - Access
- Risks of buprenorphine initiation include risk of return to use or precipitated withdrawal during transition period
- Low-dose buprenorphine initiation has evidence for efficacy; most evidence comes from hospital setting

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CASE EXAMPLE 1: OBOT PATIENT

38M with history of OUD, ventral hernia, severe vision impairment, unhoused, presenting to low-barrier OBOT clinic for restart of buprenorphine.

Last seen in OBOT clinic in 2021, prior history of heroin use and started on buprenorphine-naloxone, previously stable on 16 mg daily. Since then, moved to Olympia, began use of fentanyl blues about 1.5 years ago (and stopped heroin). Now taking 15-20 blues daily, occasional fentanyl powder. Has returned to Seattle, staying in tent. Wants to stop fentanyl use. Doesn't have money to continue buying fentanyl.

Tried to quit fentanyl and start buprenorphine-naloxone (purchased from street) but unsuccessful in the last few weeks. Says that prior successful approach to bup initiation (taking 1-2 Suboxone strips [8-16 mg bup] BID about 24 hours after last use of heroin) hasn't been successful with fentanyl, and sent him into precipitated withdrawal, even when waiting 2 days from last use of fentanyl.

Asks for your help with restarting buprenorphine-naloxone.

- **How can you counsel this patient on approaches to starting buprenorphine? What more information might you need?**
- **What are some pros and cons to traditional, low-, and high-dose initiation approaches?**

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CASE EXAMPLE 1: OBOT PATIENT

Buprenorphine Initiation Approach	Pros	Cons
Traditional	Simpler instructions Can stop using opioids right away	Already tried it, didn't work due to precipitated withdrawal
Low-Dose	Minimizes withdrawal risk	Requires continued fentanyl use ($$ is a concern) Complex titration instructions, takes a week or more Vision impairment
High-Dose	Simpler instructions Fastest method to get onto bup Can stop using opioids right away	Risk of precipitated withdrawal Patient concerned about GI side effects (with history of ventral hernia) Least evidence/experience

- In the end, patient opted for low-dose buprenorphine-naloxone initiation.
- Buprenorphine-naloxone prescribed, with comfort medications to use PRN (clonidine, gabapentin, ondansetron)
- Naloxone kit given to patient
- Follow-up is scheduled for this week, outcome TBD!

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CASE EXAMPLE 2: HOSPITALIZED PATIENT

- 65M history of OUD, gastric adenocarcinoma s/p resection complicated by severe anastamosis stricture, presenting with recurrent stricture resulting in acute on chronic abdominal pain and malnutrition.
- Smoking 10 fentanyl "blues" daily previously.
- Methadone started at 30 mg daily, increased to 35 mg daily
- However complicated by intermittently prolonged QTc >500
- Risk/benefit discussion with patient:
  - Patient willing to transition to buprenorphine
  - Motivated by desire to travel, felt monthly visits to clinic more feasible than frequent OTP clinic visits
  - Risks of precipitated withdrawal discussed

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CASE EXAMPLE 2: HOSPITALIZED PATIENT

Day	Buprenorphine	Methadone	Notes
0	None	35 mg daily	No withdrawal symptoms
1	Buprenorphine 450 mcg buccal once	35 mg daily	“Irritability”
2	Buprenorphine 450 mcg buccal BID	35 mg daily	No change in symptoms
3	Buprenorphine 900 mcg buccal BID	35 mg daily	No change in symptoms
4	Buprenorphine-naloxone 2-0.5 mg SL BID	35 mg daily	No change in symptoms
5	Buprenorphine-naloxone 4-1 mg SL BID	35 mg daily	Restlessness, rhinorrhea
6	Buprenorphine-naloxone 8-2 mg SL BID	None	Irritability, anxiety, restlessness, rhinorrhea
7	Buprenorphine-naloxone 8-2 mg SL BID	None	Nausea, diarrhea, but otherwise better

Patient ultimately transitioned to XR buprenorphine 300 mg SC injection by day 10
Discharged with OBOT clinic follow-up for buprenorphine monthly injections

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Thank you!

Amy Liu

amy.liu@case.edu

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- Jocelyn James, MD
- Joseph Merrill, MD, MPH
- Jamie Darnton, MD
- Addy Adwell, RN-BC, BSN
- UW Addiction Medicine Fellowship

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