Buprenorphine in Primary Care

In the Era of Fentanyl

DATE: April 19th, 2024 Presented by: Julie Byler, D.O., FASAM

Disclosures

- No financial disclosures
- Will be talking about some uses of buprenorphine outside of FDA approved package insert

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Learning Objectives

- Discuss the recent rise in fentanyl use and how this impacts management of opioid use disorder
- Explain the benefits of medications for opioid use disorder (MOUD)
- Describe the pharmacology of buprenorphine
- Identify when and how to prescribe buprenorphine, including various buprenorphine induction methods
- Discuss some new buprenorphine management strategies in the era of fentanyl

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Buprenorphine Knowledge Check-In

Background: The Current Environment and Fentanyl

Fentanyl Now Primary Opioid Being Used

- Fentanyl use progressively increasing since ~2013
- Patients using illicit opioids now **almost exclusively using fentanyl and/or synthetic fentanyl analogues**
- In almost all states, fentanyl is primary opioid used and leading cause of opioid related deaths

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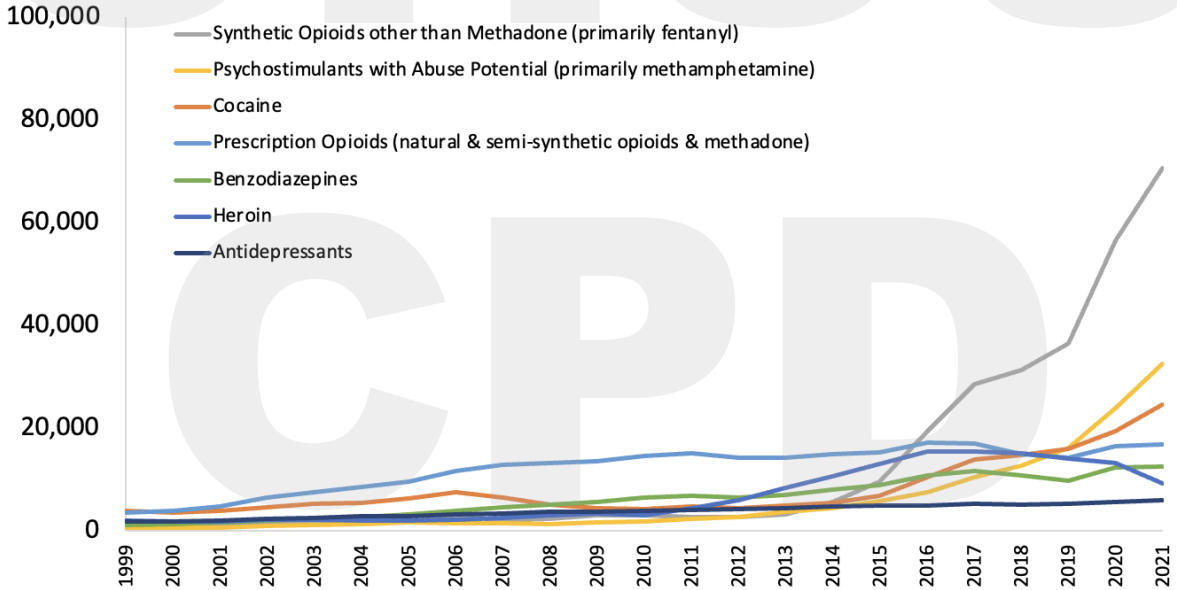
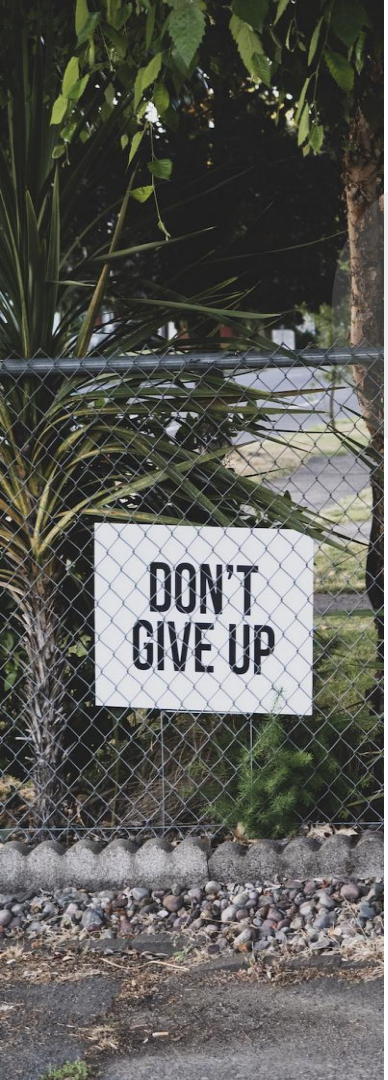
Fentanyl Primary Driver of Increase in Overdose Deaths

Figure 2. National Drug-Involved Overdose Deaths*, Number Among All Ages, 1999-2021



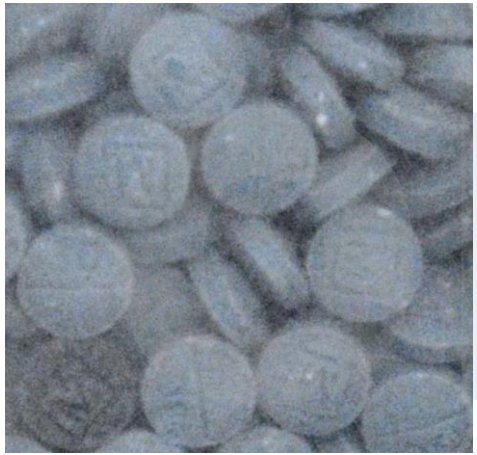
CDC WONDER/NIDA 2023[1]

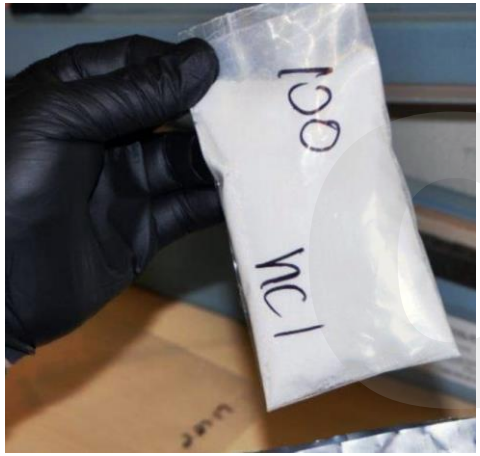


What's Different About Fentanyl?

- Different analogues have different potency and pharmacokinetics
- In general:
  - **Very potent – about 40 times more potent than heroin**
  - Short half-life, but **very lipophilic**
    - **with repeated use, accumulates and acts more like long-acting opioid**
    - **fast uptake into CNS → more reinforcing**

Volkow 2021[9]
Ahmed et al. 2020[10]





Images Courtesy of DEA
https://www.dea.gov/galleries/drug-images/fentanyl

How is Fentanyl Used?

- Sold primarily as blue pills (“blues”) or powder
- Use patterns vary by region – here, primarily being used via inhalation

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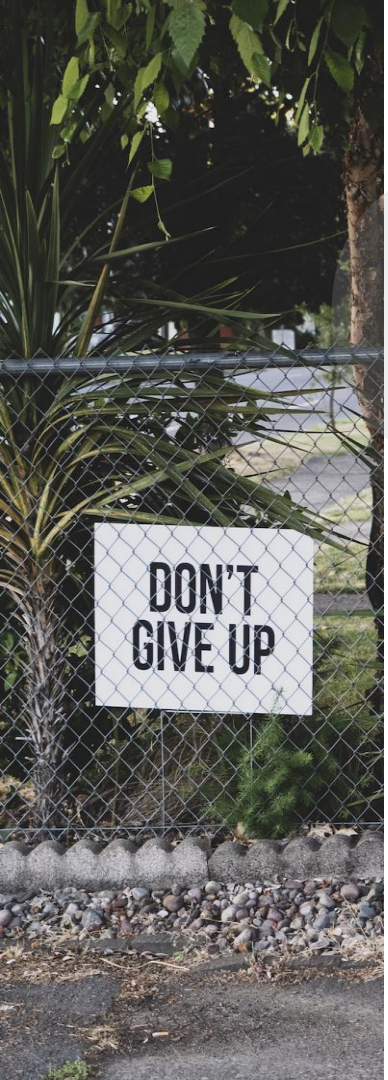
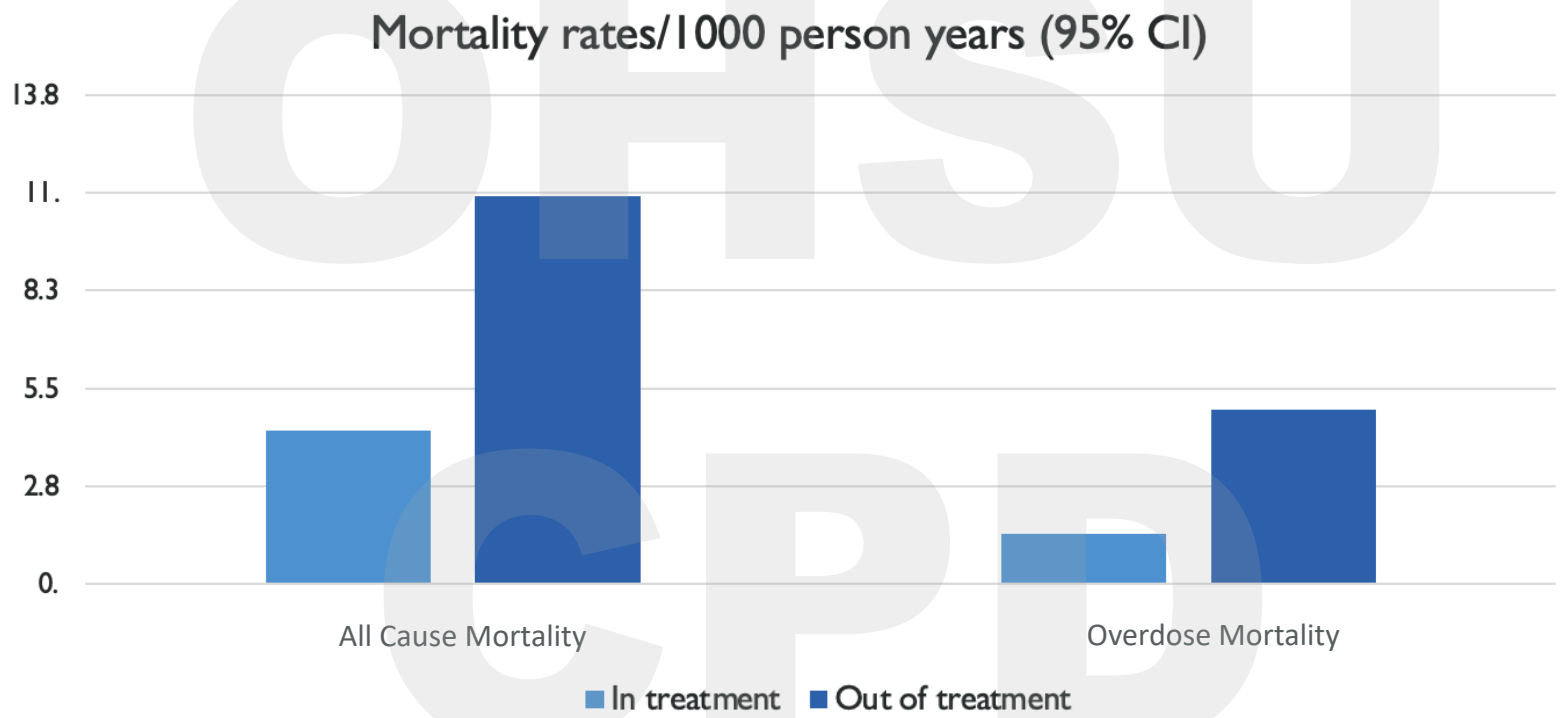
How We Can Help



Medications for Opioid Use Disorder (MOUD)

- First line treatment for opioid use disorder (OUD)
- Three FDA approved medications
  - **Buprenorphine (partial opioid agonist) – focus of today**
  - Methadone (full opioid agonist)
    - Only dispensed through opioid treatment programs
  - Naltrexone (opioid antagonist)
    - Requires period of abstinence from opioids before starting (difficult in patients with active use)

MOUD Saves Lives



Sordo et al. 2017[5]

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Why Prescribe MOUD?

- In addition to decreased mortality:
- **Decreases risk of overdose and infectious complications**
- **Increases rates of abstinence and retention in treatment[3]**
  - Number need to treat (suppression of illicit opioid use) = 2
- Lower than MANY medications we commonly prescribe
  - NNT=104 for statins

Mattick et al. 2013[3]

How Does Buprenorphine Work?

- **Partial agonist at mu opioid receptor**
  - Treats withdrawal symptoms, cravings
  - Blocks reinforcing effects of ongoing opioid use
  - STRONG binding affinity
    - Can precipitate withdrawal if using other opioids
  - **Safe → Ceiling effect on respiratory depression** and evidence shows it **reduces risk of overdose**

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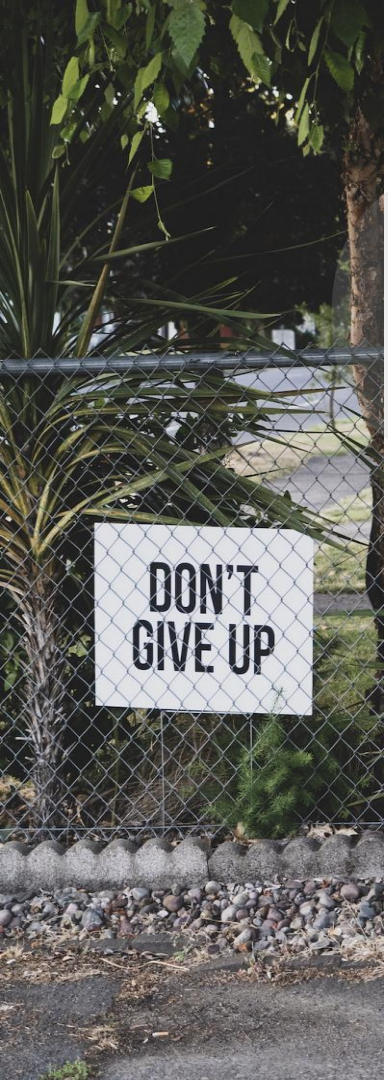
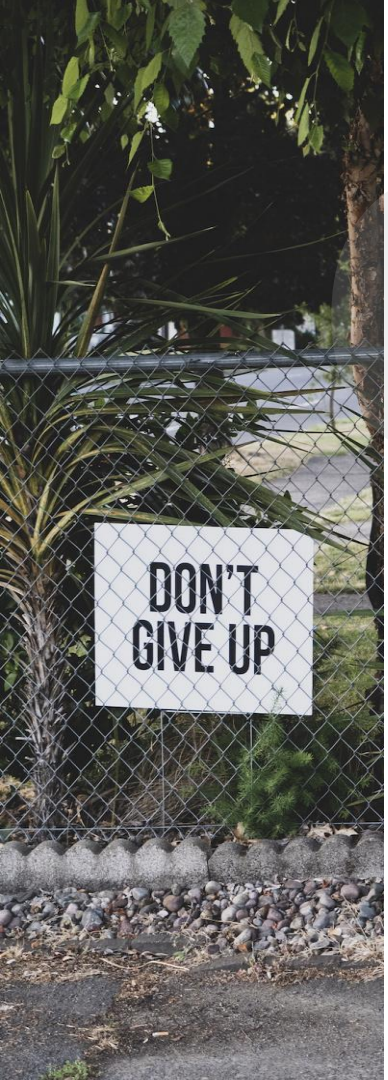


Buprenorphine Formulations

- **Sublingual**
  - Most common
  - Buprenorphine (“Subutex®”)
    - Tablets
  - Buprenorphine/naloxone (“Suboxone®”)
    - Naloxone **inactive** when taken SL
    - Tablets and films
  - Tablets and films can be split if needed
  - Defer to patient preference/insurance coverage when choosing

Buprenorphine Formulations

- **Extended Release (XR) Buprenorphine**
  - Subcutaneous, depot injection
  - Includes
    - Sublocade®
    - BRIXADI™ (NEW)
- Transdermal Patch (Butrans®)
  - FDA approved for treatment of chronic pain
- Buccal Film (Belbuca®)
  - Also approved for chronic pain only



Dosing Schedules

- Sublingual
  - Per patient preference
  - Once daily, up to four times daily
    - Split dosing may be better for pain management

- Extended-Release Depot
  - Once a month (q28 days) for Sublocade®
  - Weekly OR monthly for BRIXADI™

Starting Buprenorphine

Can I Prescribe Buprenorphine?

- **Yes!**
- Used to require X-Waiver and were limits on number of prescriptions
- **X-waiver is no longer required - any physician with a DEA license can now prescribe**
  - All providers applying for a DEA license now required to do 8-hr training on how to manage pain and treat patients with substance use disorders

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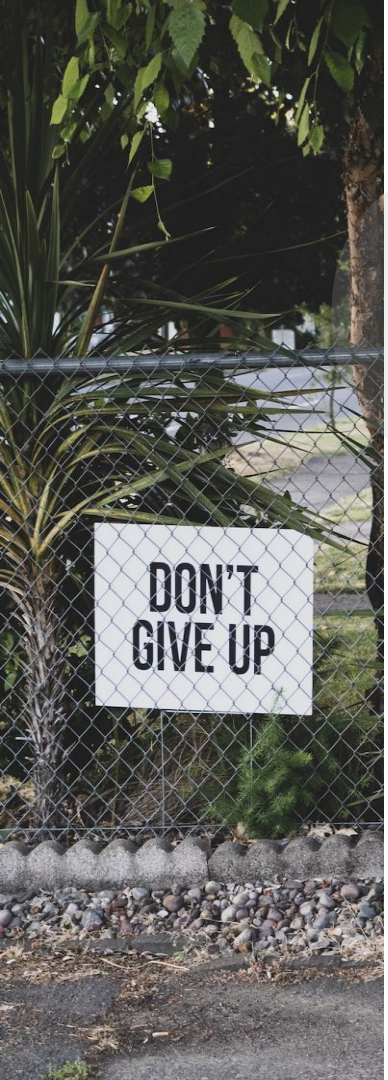

When Should I Consider Prescribing Buprenorphine?

- To treat symptoms of **opioid withdrawal**
- In patients with **moderate to severe opioid use disorder**
  - Diagnosed with DSM V criteria

When to Screen for Opioid Use Disorder

- Opioid withdrawal symptoms
- Skin and soft tissue infections
- Endocarditis
- Flu like symptoms
- Nausea/vomiting/diarrhea
- History of HIV or HCV
- Positive urine toxicology
- Use of alcohol or other substances

DSM V Criteria for OUD

Check all that apply

	Opioids are often taken in larger amounts or over a longer period of time than intended.
	There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
	A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
	Craving, or a strong desire to use opioids.
	Recurrent opioid use resulting in failure to fulfill major role obligations at work, school or home.
	Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
	Important social, occupational or recreational activities are given up or reduced because of opioid use.
	Recurrent opioid use in situations in which it is physically hazardous
	Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids.
	*Tolerance, as defined by either of the following: (a) a need for markedly increased amounts of opioids to achieve intoxication or desired effect (b) markedly diminished effect with continued use of the same amount of an opioid
	*Withdrawal, as manifested by either of the following: (a) the characteristic opioid withdrawal syndrome (b) the same (or a closely related) substance are taken to relieve or avoid withdrawal symptoms

Total Number Boxes Checked: _____

Severity: **Mild**: 2-3 symptoms. **Moderate**: 4-5 symptoms. **Severe**: 6 or more symptoms

*Criteria from American Psychiatric Association (2013). Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,. Washington, DC, American Psychiatric Association page 541. For use outside of IT MATTTRs Colorado, please contact ITMATTTRsColorado@ucdenver.edu

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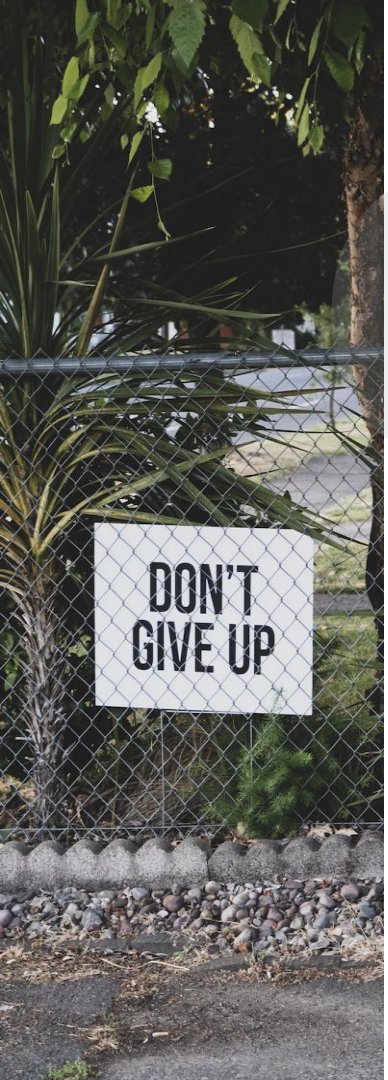

Recognizing Opioid Withdrawal

- Objective signs:
  - Tachycardia, diaphoresis, restlessness, **dilated pupils**, **rhinorrhea or lacrimation**, vomiting, diarrhea, **goosebumps, yawning.**
- Subjective signs:
  - Nausea, stomach cramps, body aches, achy joints, restlessness, anxiety, hot/cold flashes, nasal congestion

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COWS (Clinical Opioid Withdrawal Scale: identifies and measures severity of opioid withdrawal

Clinical Opioid Withdrawal Score (COWS)

5-12 mild 13-24 moderate 25-35 moderately severe 36+ severe

Signs or symptoms	Score
Resting pulse rate: Measured while patient resting for 1 minute	0 = 80 or below 1 = 81 to 100 2 = 101 to 120 4 = greater than 120
Sweating: Not accounted for by patient activity or room temperature	0 = no reports of chills or flushing 1 = subjective report of chills or flushing 2 = flushed or moistness on face 3 = beads of sweat on brow or face 4 = sweat streaming off face
Restlessness: Observation during assessment	0 = able to sit still 1 = reports difficulty sitting still, but is able to do so 3 = frequent shifting or extraneous movement of legs/arms 5 = unable to sit still for more than a few seconds
Pupil size:	0 = pinned or normal for room light 1 = possible larger than normal 2 = moderately dilated 5 = Only rim of the iris visible
Bone or joint pain: Not associated with injury or chronic pain	0 = not present 1 = mild diffuse discomfort 2 = severe diffuse aching 4 = rubbing joints and muscles due to pain
Rhinorrhea or lacrimation:	0 = not present 1 = Nasal stuffiness or unusually moist eyes 2 = rhinorrhea or lacrimation present 4 = constant rhinorrhea or tears running down face
GI upset: in last half hour	0 = no GI symptoms 1 = stomach cramps 2 = nausea or loose stool 3 = vomiting or diarrhea 5 = multiple episodes of vomiting or diarrhea
Tremor: Observation of outstretched hands	0 = no tremor 1 = Tremor felt but not observed 2 = slight observable tremor 4 = gross tremor
Yawning:	0 = no yawning 1 = once or twice 2 = three or more times 4 = several times/minute
Anxiety/irritability:	0 = none 1 = patient reported 2 = obvious 4 = severe enough to interfere with assessment
Piloerection:	0 = skin is smooth 3 = piloerection can be felt or hairs standing up on arms 5 = prominent piloerection

Picture courtesy of Taming the SRU blog[8]

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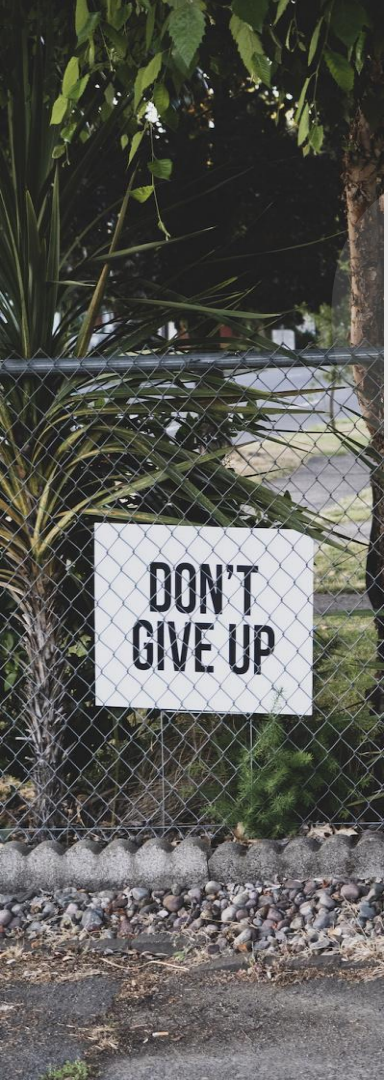


Prior to Initiation

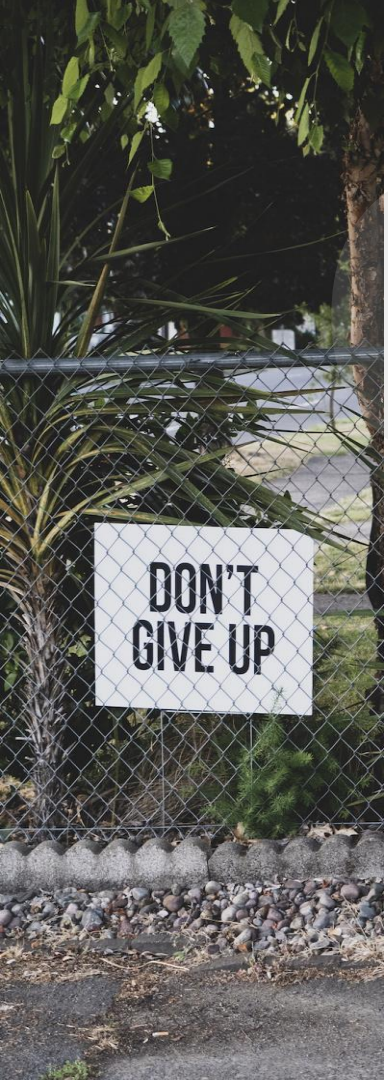
- Screen for other substance use
  - Co-ingestion of benzodiazepines or alcohol increases risk of adverse effects incl overdose
- Patient counseling and education
  - Benefits, side effects and alternatives
  - **Increased risk of overdose if buprenorphine is stopped**
  - Withdrawal if stopped abruptly
  - **Induction process incl. risk of precipitated withdrawal**
  - How to properly take (see later slide for details)
- Check PDMP
- Fentanyl Use?

Fentanyl Has Made OUD Treatment More Difficult

- **Why?**
  - **Potency** - when used regularly can cause **very high opioid tolerances**
    - **Harder to get patients stabilized on MOUD**
  - Short acting and causes severe withdrawal - people feel sicker sooner, use more frequently, more reinforcing
  - **Accumulates with repeated use → must wait a lot longer before standard induction, more precipitated withdrawal**
    - **Consider alternative/novel induction strategies**

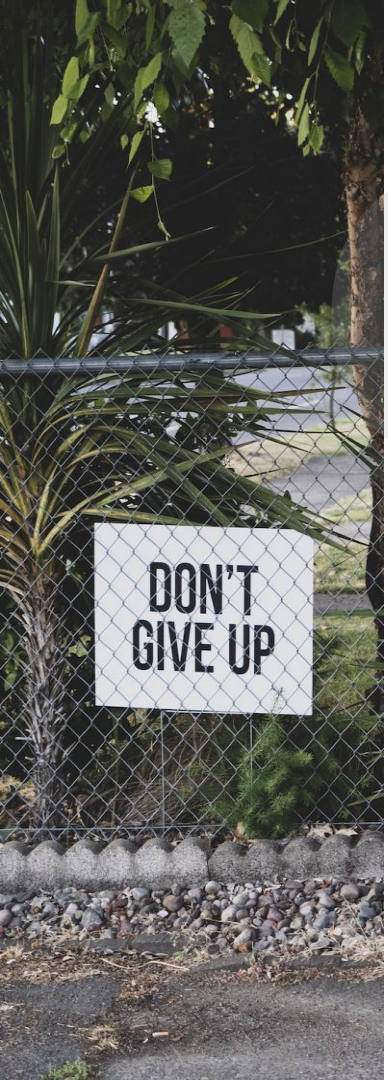
Induction Basics

- Partial agonist with **HIGH opioid receptor affinity**
  → precipitated withdrawal if taken too soon after use of other opioids
- Need to be in **at least moderate opioid withdrawal prior to induction** (Unless doing low dose induction)
- This is usually
  - 12-24 hours after use of short-acting opioids such as heroin, oxycodone
  - **24-72 hours** after use of long-acting opioids such as **fentanyl**, methadone



Types of Inductions

- Standard induction
  - Most data, around the longest
  - **In the era of fentanyl this is challenging and often does not work well**
  - Consider in patients using short-acting, relatively lower potency opioids i.e. heroin, prescription opioids
- High dose inductions (“macro” induction)
- Low dose inductions (“micro” induction)



Standard Induction

Generally, do not recommend in fentanyl use

Day One

1. Discontinue opioid use
2. Wait until in at least moderate withdrawal (COWS > 12)
3. Give 4 mg SL buprenorphine
4. Re-evaluate after 1-2 hours, give additional 4 mg SL buprenorphine prn for ongoing withdrawal sx
5. Continue process until withdrawal symptoms improved, up to 16-32 mg

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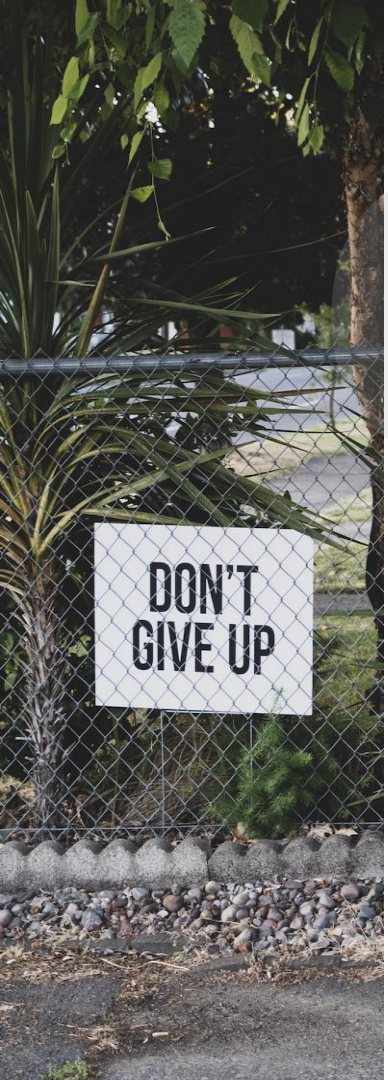
Standard Induction

Day Two

1. Take total dose from day one
2. Additional 2-4 mg SL prn for ongoing withdrawal symptoms or cravings to max daily dose 24-32 mg

Day Three On

1. Prescribe total daily dose required to adequately treat withdrawal symptoms and cravings
2. Can take once a day, or in divided doses per patient preference
3. Close follow up to ensure adequacy of dose



High Dose Induction

- Consider in patients using **fentanyl**
- Still wait until patient is in withdrawal
  - Consider higher COWS (i.e. > 14- 16) with **at least one objective sign of withdrawal** (i.e. piloerection, dilated pupils, tachycardia, rhinorrhea, yawning, restlessness)
- Uses **higher initial doses** that standard induction
  - **Start with SL 8-16 mg**
  - **Rapidly up-titrate** to effective dose **(usually 24-32 mg)**
- Idea is to get to agonism/relief of withdrawal symptoms faster

High Dose Inductions

Advantages

- **Fast**
- Reduced risk of precipitated withdrawal
- Data supports safety in patients with suspected high opioid tolerances[11]

Disadvantages

- May not be appropriate in all patients (significant medical co-morbidities, other centrally acting or sedating medications, lower opioid tolerance)
- Patients **still must go into withdrawal** prior to induction

Ahmadi et al. 2020[11]

High Dose Induction Protocol

Buprenorphine Self-Start

Guidance for patients starting buprenorphine outside of hospitals or clinics

1. Plan to take a day off and have a place to rest.
2. Stop using and wait until you feel very sick from withdrawals (at least 12 hours is best, if using fentanyl it may take a few days).
3. Dose one or two 8mg tablets or strips UNDER your tongue (total dose of 8-16mg).
4. Repeat dose (another 8mg-16mg) in an hour to feel well.
5. The next day, take 16-32mg (2-4 tablets or films) at one time.

If you have a light habit: *(For example, 5 "Norco 10's" a day)*

- Consider a low dose: start with 4mg and stop at 8mg total.
- **WARNING:** Withdrawal will continue if you don't take enough bup.

If you have a heavy habit: *(For example, injecting 2g heroin a day or smoking 1g fentanyl a day)*

- Consider a high dose: start with a first dose of 16mg.
- For most people, the effects of bup max out at around 24-32mg.
- **WARNING:** Too much bup can make you feel sick and sleepy.

CA Bridge Self-Start[7]

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High Dose Induction

"QuickStart"

- Can start anytime after last use
- Self administer naloxone → withdrawal → give SL buprenorphine 24 mg
- Expect withdrawal and may be severe, but predictable and short
- Must be able to tolerate withdrawal

TABLE 2 - Chronology of Transition From Fentanyl to Buprenorphine-naloxone

Event	Time Elapsed, min	Time Between Events, min	COWS*
Last use of fentanyl	120 min prior		0
Premedication with clonidine 0.2 mg and gabapentin 600 mg	0	120	0
4 mg (1 spray) intranasal naloxone	36	36	NS†
GI upset ("stomach not feeling right")	38	2	NS
COWS measured	42	4	9
Vomiting (2 episodes of vomitus, 3 episodes of dry heaving)	45	3	NS
24/6 mg sublingual buprenorphine-naloxone at once	50	5	28
Buprenorphine-naloxone fully dissolved. Subjective withdrawal symptoms 0–10; he states that he is at a 4. Feeling tired.	60	10	NS
Discontinued visit to sleep	65	5	NS

*Clinical Opioid Withdrawal Scale (COWS), excluding heart rate.
†COWS not scored.

Randall A et al. 2022[12]

Low Dose Induction

- Start with very low doses of buprenorphine and slowly up-titrate
  - Less abrupt displacement from opioid receptors → decreased risk of precipitated withdrawal
- **Starting doses will NOT treat withdrawal or cravings**
  - Patients continue full opioid agonist until reach therapeutic dose of buprenorphine
- **Do NOT need to go into opioid withdrawal**
- Many different protocols, no good evidence for which one works best

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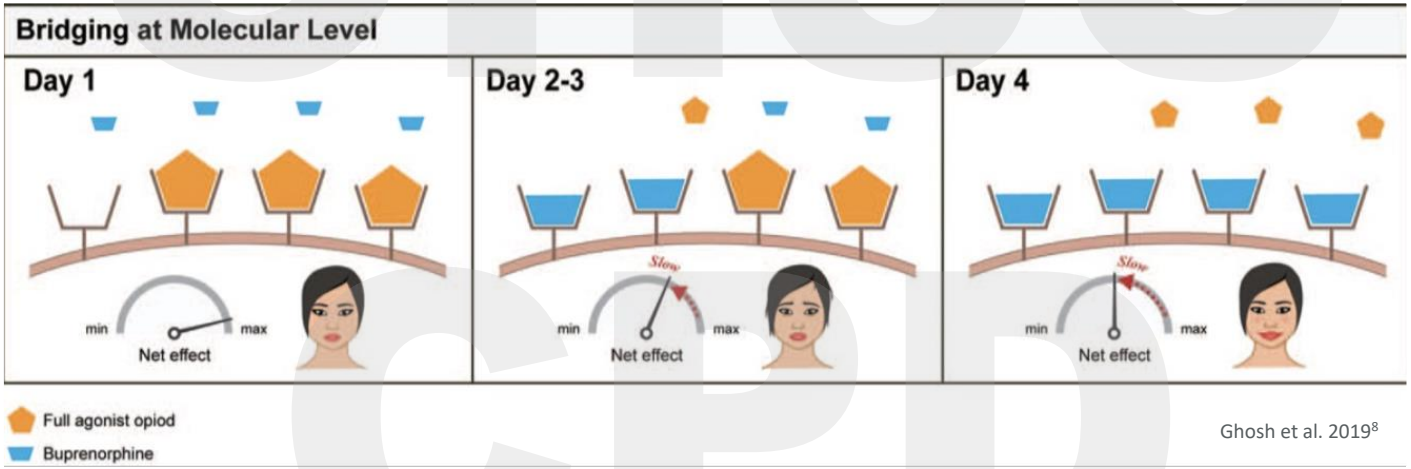
Low Dose Induction Mechanism



Ghosh et al. 2019[8]

Low Dose Induction

Advantages

- Patients **don't need to go into withdrawal** before induction
- Reduces risk of precipitated withdrawal
- Allows ongoing full agonists for pain if needed

Disadvantages

- Takes longer
- Dosing instructions usually complex, can be hard for patients to follow
- Concerns re: ongoing opioid use
- Many different protocols, unclear if some are better than others

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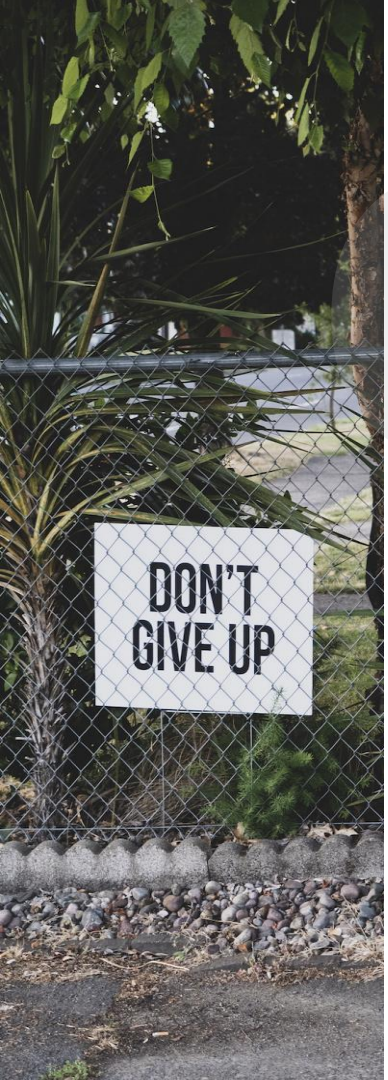
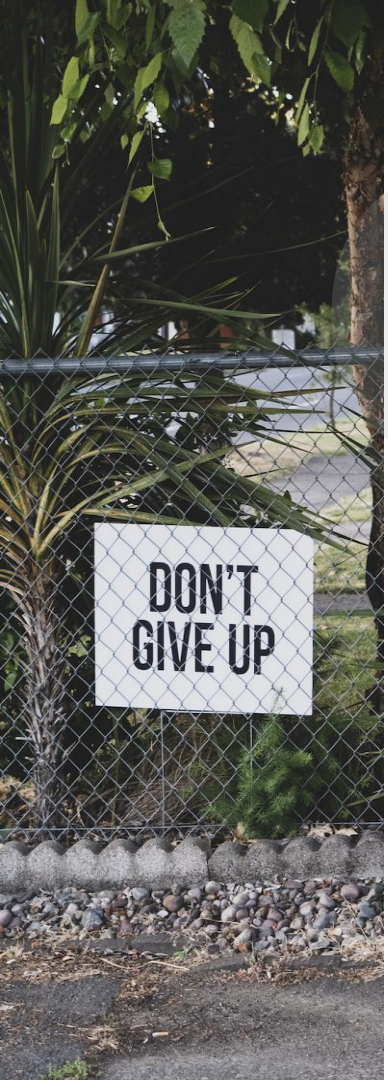


Example Low Dose Protocol

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

STOP all other full opioid agonists on Day 7

Adapted from Yale protocol



Example Low Dose Protocol

Day	Full Opioid Agonist	Buprenorphine Dosing	Total Daily Buprenorphine Dose
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	Continue	4 mg SL once. If tolerate, take additional 4-8 mg SL q1-2 hrs for ongoing cravings/withdrawal up to 16-32 mg	4-32 mg

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Low Dose Induction Tips and Tricks

- Dosing is complicated
  - **Good patient instructions are very helpful**
  - **Consider blister packs**
- **Close follow up**
- Prescribe adjuncts and explain how/when to use them
- Slow down or repeat days if needed
- If still not going well, consider
  - Switching to high dose induction
  - Referring to inpatient management

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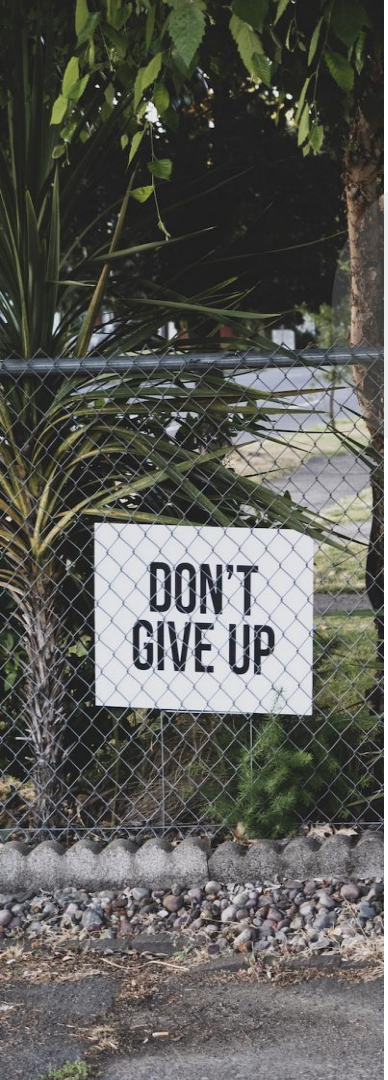
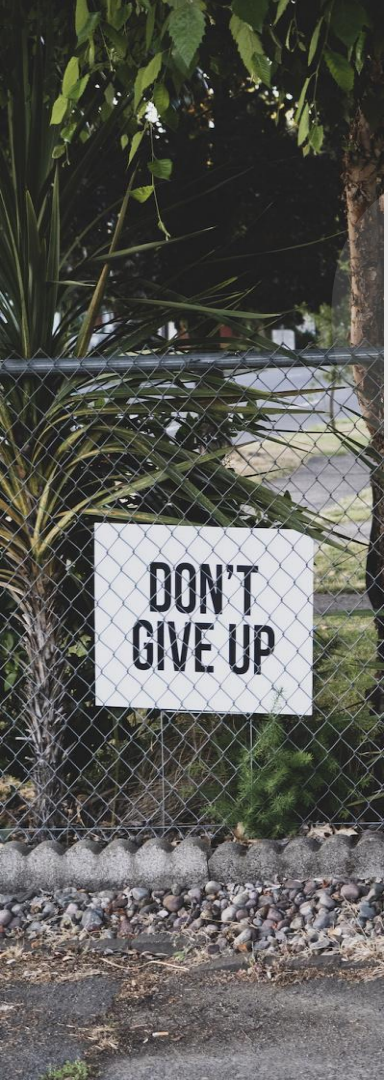


Adjunct Medications

- Prescribe for ALL patients if no contraindications
- If patient is using fentanyl, **consider scheduling rather than having prn and pre-medicating before first dose of buprenorphine**

Medication	Opioid withdrawal symptom
Clonidine 0.1-0.2 mg po q 6 hours prn	Restlessness, anxiety
Tizanidine 2-6 mg po q 6 hours prn	Muscle cramps, all over body pain
Hydroxyzine 25-100 mg po q 6 hours prn	Anxiety, restlessness
Trazodone 25-100 mg po qhs prn	Insomnia
NSAIDS, tylenol- consider scheduling	Pain
Zofran 4-8 mg po q 6 hours prn	Nausea, vomiting
Loperamide 2-4 mg po q 4-6 hours prn	Diarrhea



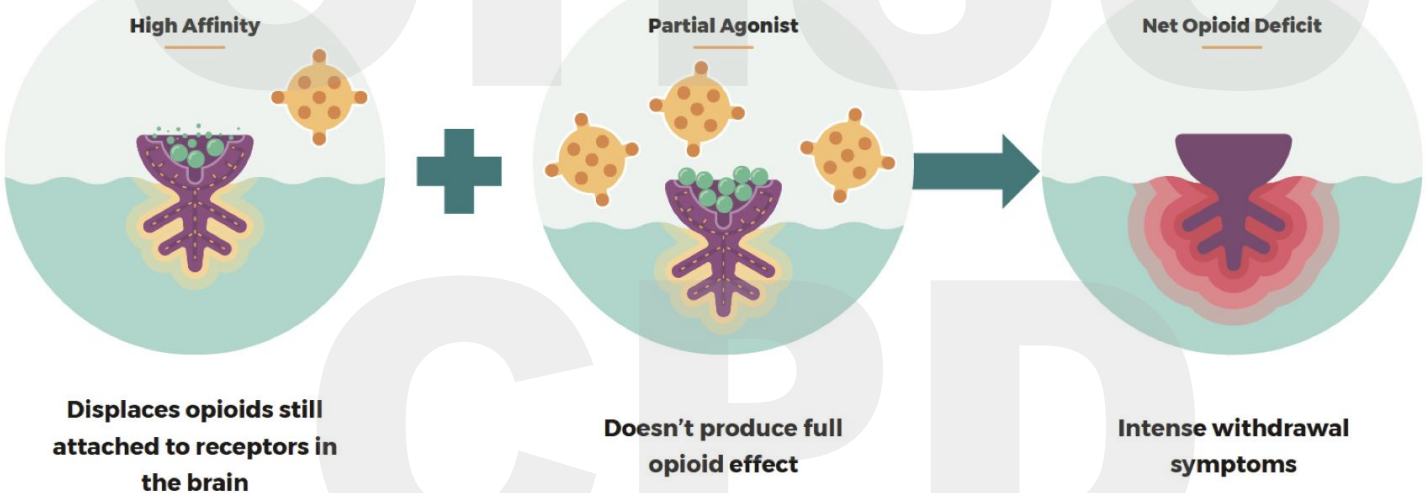
Choosing an Induction Protocol

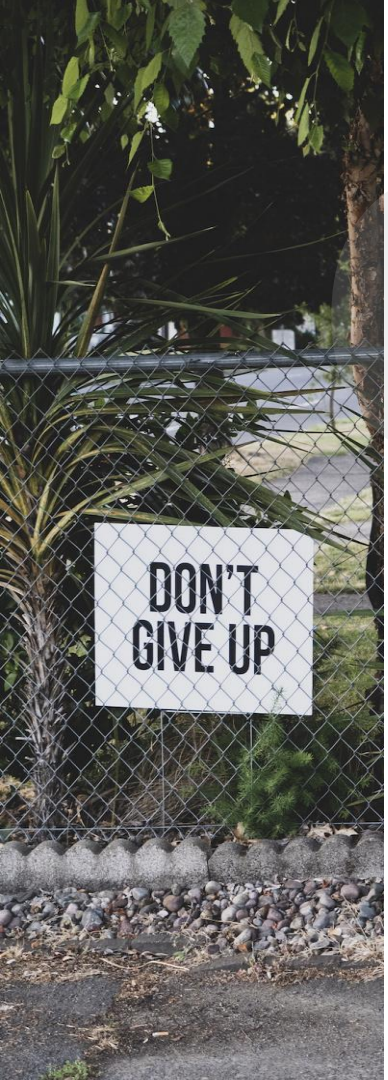
- Should be **individualized and patient centered**
- If using heroin or short acting prescription opioids → consider standard induction
- If using fentanyl, consider:
  - **If they have done an induction before – if it worked well, do the same thing, if not try something different**
  - Willing to go into withdrawal? If no, consider low dose
  - Ability to follow complex dosing? If no, low dose might not be best option

Precipitated Withdrawal

- Often provider and patient's biggest concern
- What it is
  - **Sudden, severe opioid withdrawal symptoms after taking buprenorphine (or opioid antagonist)**
  - Caused by displacement of other opioids from opioid receptors
  - Usually occurs within 30 mins after dose
  - **Not subtle** and patients will know if this happens
  - Techniques to avoid include novel induction strategies, ensuring in enough withdrawal before first dose

Mechanism of Precipitated Withdrawal





Treating Precipitated Withdrawal

- **More buprenorphine!**
  - **→ more opioid agonism → eventual relief of withdrawal symptoms**
  - Seems counterintuitive, so should educate patients on this BEFORE they do the induction
  - Give adjunct medications
    - **Including consideration of low dose benzodiazepines in appropriate patients**

Buprenorphine Maintenance Dosing

- Historically, max daily dose was 24 mg
- Not enough for a lot of patients in the era of fentanyl
- **Now, usually use 32 mg max daily dose**
  - Covered by OHP for all patients, no longer need a prior authorization
  - Evidence has shown this is safe
  - **Titrate to effect with low threshold to go up to 32 mg, especially in the first few days**

Buprenorphine Maintenance Doses

Retention increased linearly with higher doses and was highest at doses of 30-32 mg

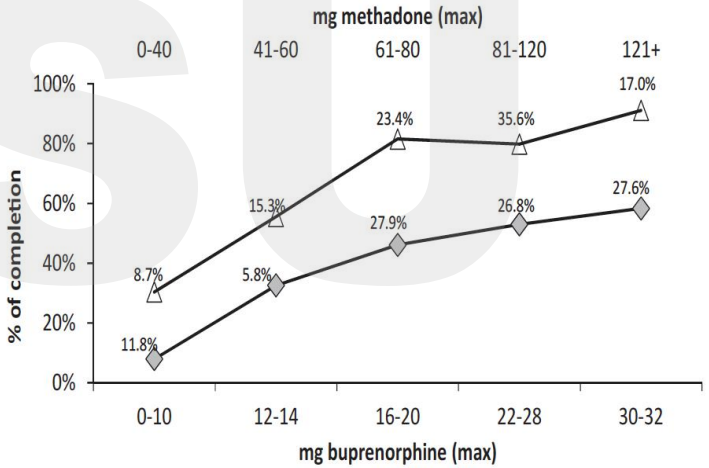


Figure 2 Comparing retention at 24 weeks by maximum dose of medication prescribed

Hser et al. 2014[13]

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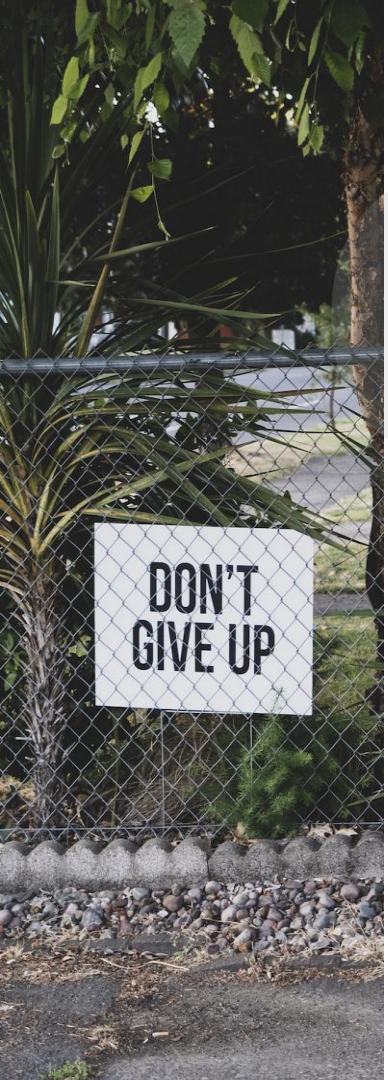

How to Take Sublingual Buprenorphine

- Counsel ALL patients on this
- If patients do not take it correctly, they will not absorb the medication
- Instructions
  - Place tablet or film under the tongue
  - Absorbs easier with moist mouth
  - Let it **completely dissolve, this takes at least 10 minutes, up to 30**
  - No drinking, eating, smoking, talking during

Extended-Release Buprenorphine

VERY Brief Overview

- Sublocade® and BRIXADI™ (approved May 2023)
- Subcutaneous depot injections
- Sublocade® is given once a month
  - 300 mg and 100 mg doses
  - 300 mg x at least 2 doses, decrease to 100 mg once stable
- BRIXADI™ has both weekly and monthly dosing, numerous doses of each, much more flexibility
- Takes time to reach steady state, many patients continue to need SL especially at the beginning

Extended-Release Buprenorphine

- Higher serum levels than SL buprenorphine
- Consider discussing as an option with all patients, but particularly for:
  - Patients with hx of overdose
  - Patients with difficulty following up/making appointments
  - Patients with ongoing cravings/withdrawal with SL buprenorphine

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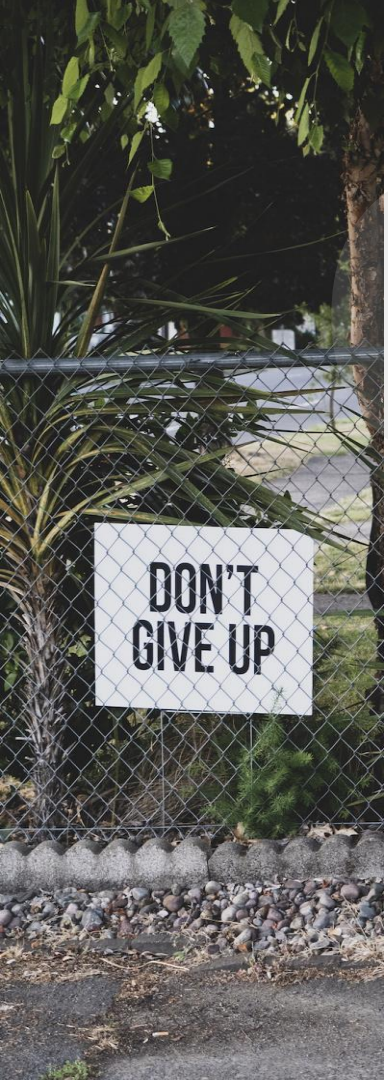

Other Best Practices

- **Prescribe naloxone to ALL patients**
- Infectious disease screening for all patients with substance use disorders incl. HIV, HCV, STI testing
- Close follow up
- Start with shorter prescription durations (i.e. 7 days), extend as patient becomes more stable
- **Instruct patients to keep medication safe and locked**
- Offer referrals to behavioral treatment

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What if Buprenorphine Doesn't Work?

- Buprenorphine is a great option for most patients
- BUT some patients have difficulty with induction process or with finding an adequate dose
- **If this happens, options include:**
  - Trying a different induction strategy
  - Increasing dose, switching to XR formulation
  - Inpatient management
  - Referral to OTP for methadone maintenance – may be the only thing that will work for patient

Additional Resources

1) SAMHSA has some great resources including buprenorphine quick start guides. https://www.samhsa.gov/sites/default/files/quick-start-guide.pdf
2) CA Bridge Clinic also has great provider resources that are free to access including patient handouts and protocols. https://bridgetotreatment.org/addiction-treatment/ca-bridge/
3) Oregon ECHO programs

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Addiction Medicine ECHO Programs

Spring Addiction Medicine Programs

- SUD in Adolescents
- SUD in Pre- and Perinatal Care

Pre-Register Now for These Programs

- SUD in Ambulatory Care
- SUD in Jails
- Addiction Medicine Curbsides and Conversations
- Hepatitis C Community of Practice

Learn more and register here

Oregon ECHO Network

Thank You!

Please provide feedback by scanning QR code below

Don’t hesitate to reach out to me at byler@ohsu.edu with any questions or concerns

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