High and Low Dose Buprenorphine Initiations – Practical Tips for the Primary Care Clinician

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June 21, 2024

Topics For Today

- Buprenorphine Initiation in the Era of Fentanyl
- Collaborative Initiation Strategies for Buprenorphine
- Low-Dose Initiation
- High-Dose Initiation
- Use of Adjunctive Medications

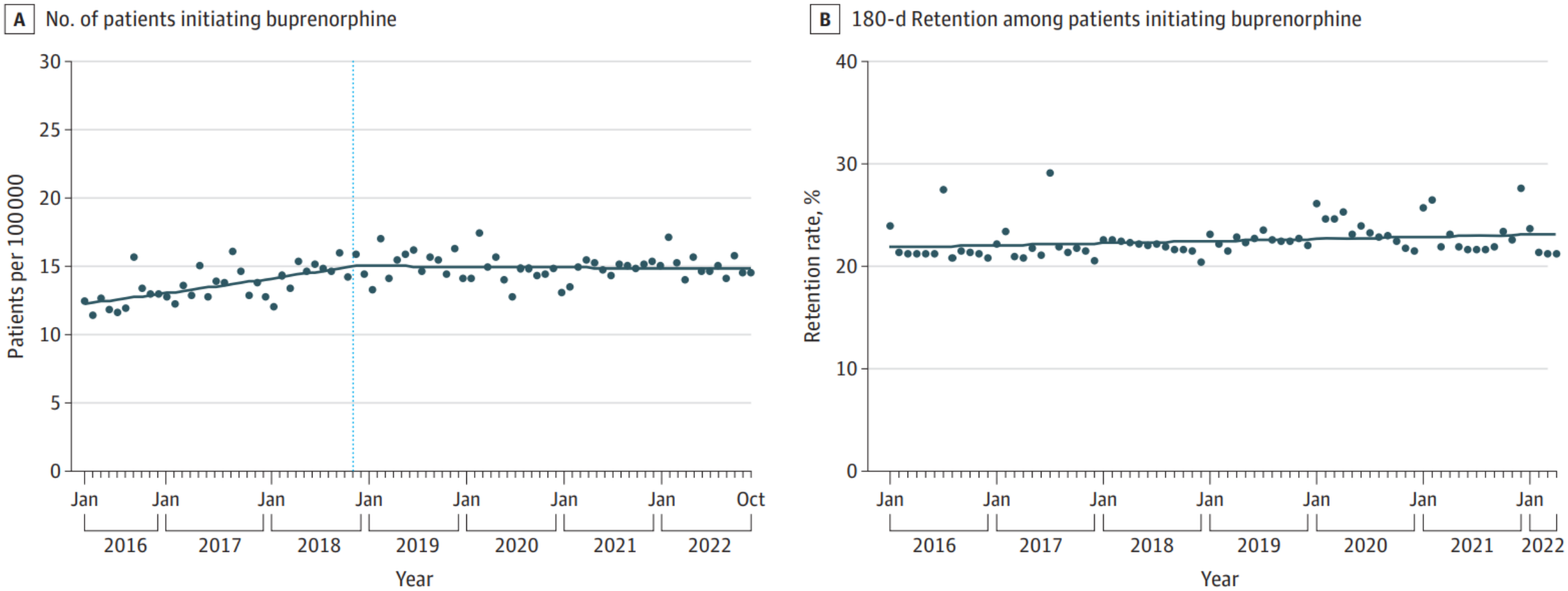
Research Letter

April 25, 2023

Trends in Buprenorphine Initiation and Retention in the United States, 2016-2022

Kao-Ping Chua, MD, PhD[1]; Thuy D. Nguyen, PhD[2]; Jason Zhang, BS[1]; et al

Figure. Monthly Trends in Buprenorphine Initiation and Retention in the US, January 2016 Through October 2022



Why the Plateau?

Fentanyl

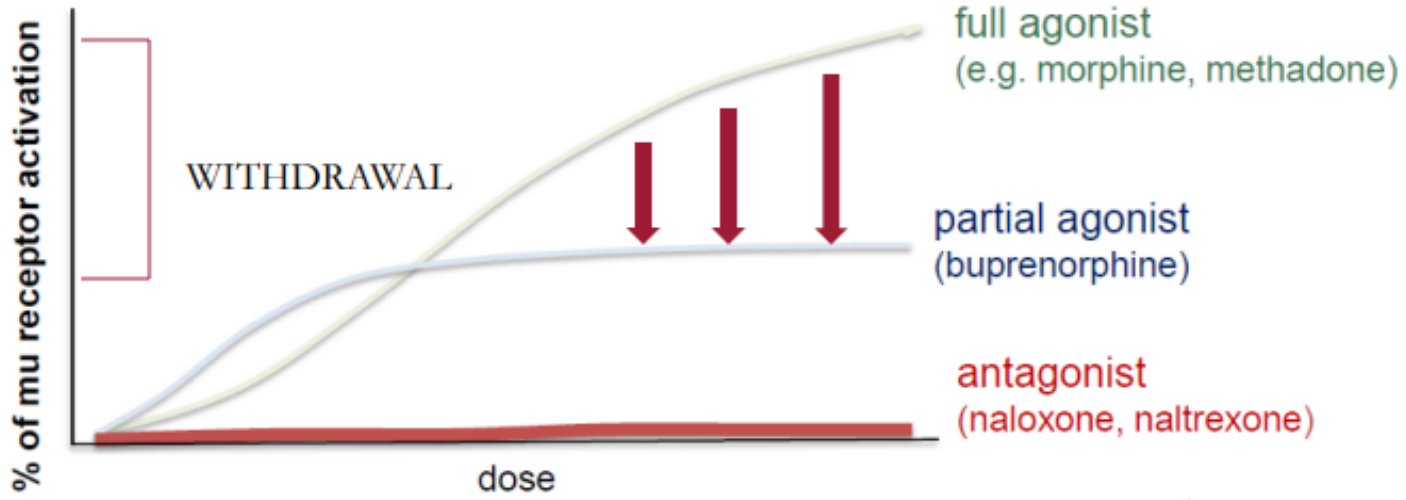
Fentanyl is 50 to 100 times more potent than morphine and 30 to 50 times more potent than heroin.

Why is it hard to get onto Buprenorphine Now?

Precipitated Withdrawal

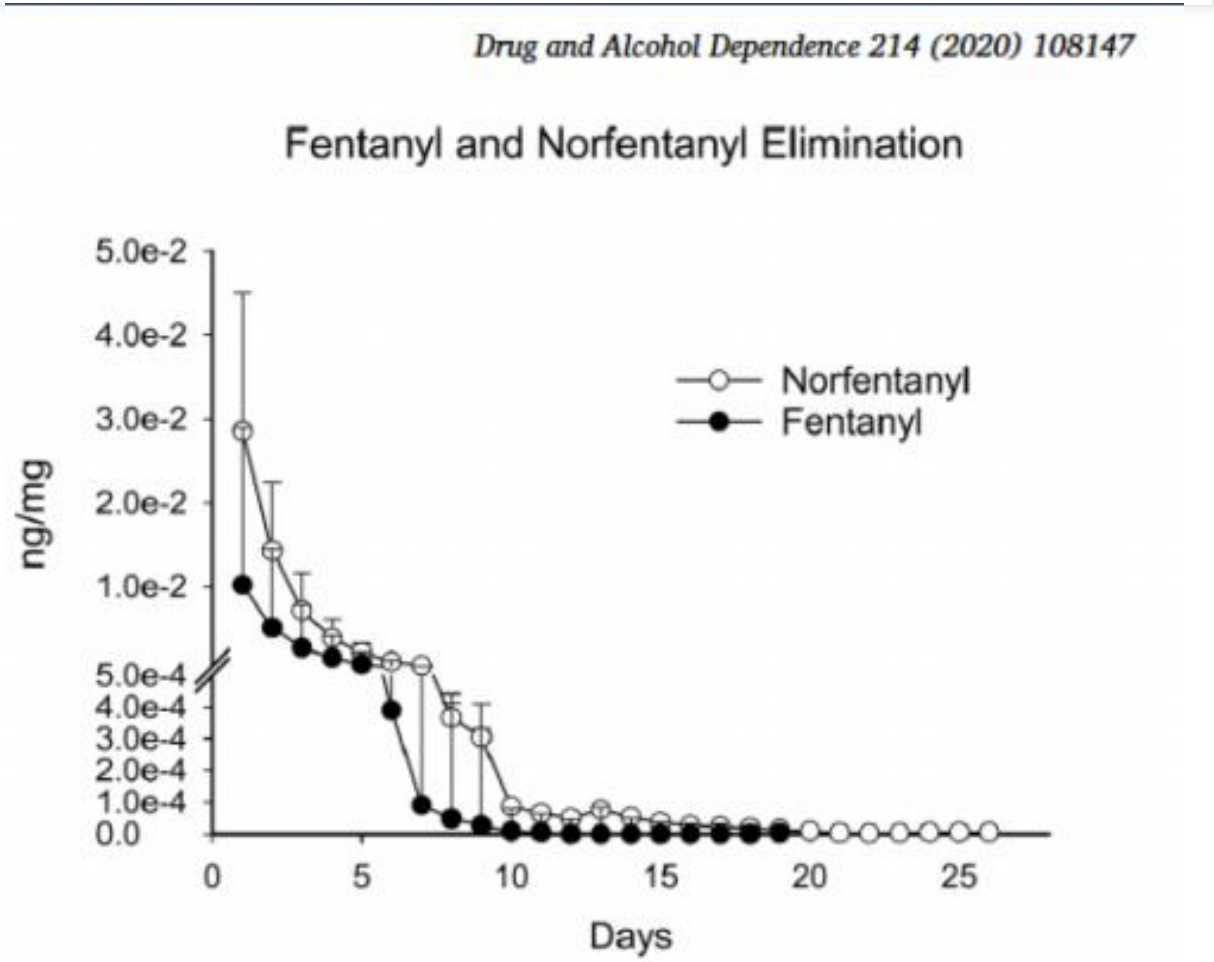
Precipitated Withdrawal

- Because of its high affinity for mu receptors, buprenorphine can replace other agonists (fentanyl, methadone) that are already present
- The sudden drop from full agonist to partial agonist stimulation of opioid receptors can cause sudden and severe withdrawal symptoms, known as precipitated withdrawal

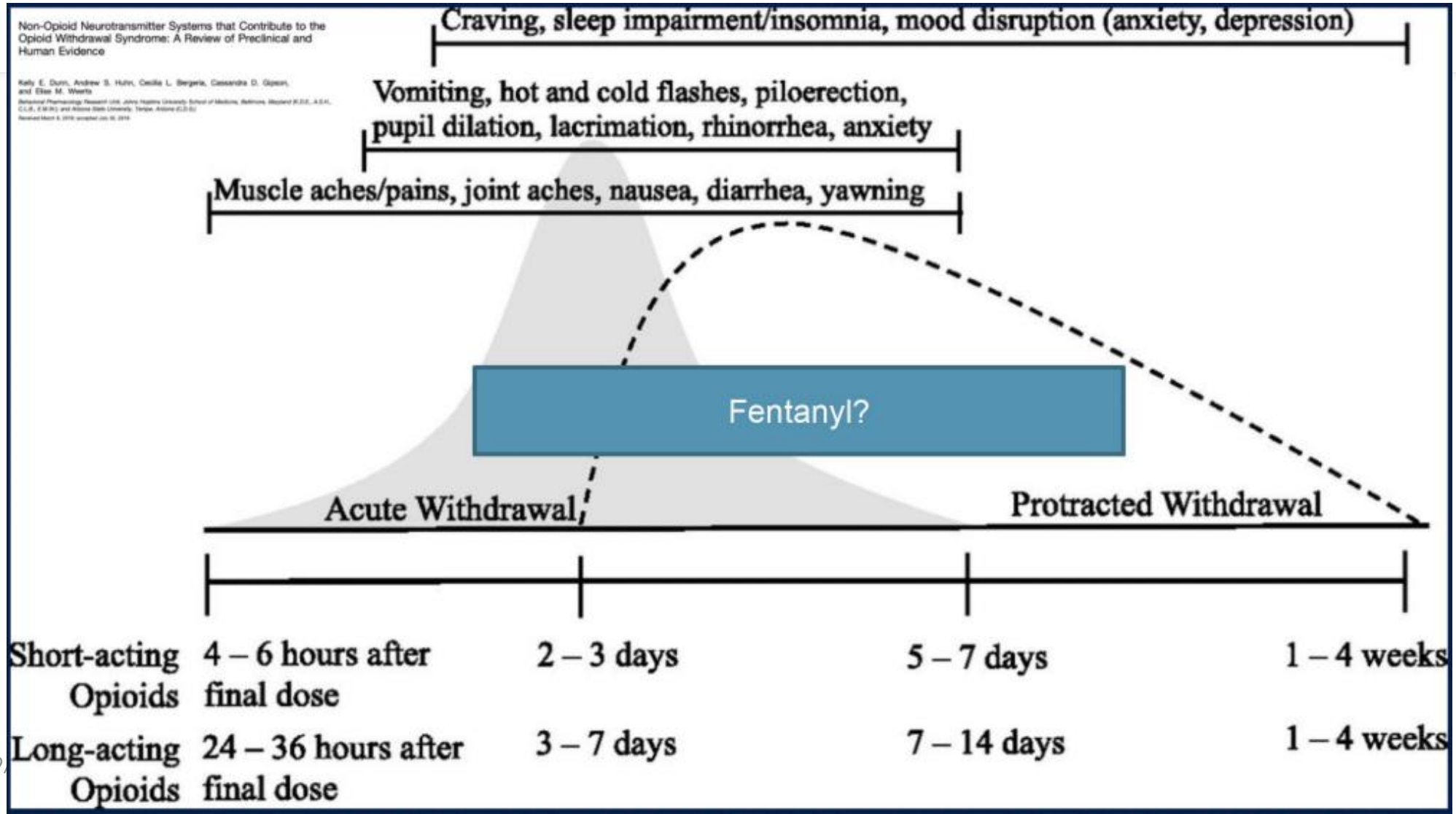


The Arrival of “Fentanyls” - Prepare For Discomfort

- Full agonist at mu opioid receptor, high binding affinity
- High lipophilicity:
  - Quickly crosses blood-brain barrier
  - Can be sequestered in adipocytes or other tissues
- Single use has short half-life (fast on, fast off) but repeated use leads to:
  - Accumulation in adipose tissue
  - Decreased renal clearance
  - *mu opioid receptor desensitization*
- This means for chronic use:
  - Mean elimination is 7.3 days for fentanyl
  - Mean elimination for norfentanyl is 13.3 days



Typical Withdrawal Course



Variable Withdrawal and Initiation Course

- Withdrawal typically starts faster and is much more intense
- Because of fentanyl's lipophilic nature, the period of withdrawal needed before buprenorphine initiation to avoid risk of precipitated withdrawal *lasts longer*
- Withdrawal symptoms can return hours or days after initiation
- Withdrawal symptoms can have very different characteristics

What Our Patients are Experiencing

"Everything is not right anymore" Buprenorphine experiences in an era of illicit fentanyl

Sydney M. Silverstein[a], **Raminta Daniulaityte**[b], **Silvia S. Martins**[c], **Shannon C. Miller**[d,e], **Robert G. Carlson**[f]

NPFs and buprenorphine experiences: Sabotaging self-treatment

While the use of non-prescribed buprenorphine helped some participants adjust to a new risk environment, others found that established practices of harm reduction and self-treatment with non-prescribed buprenorphine were challenged by the takeover of NPF. Gaia, a 32-year old woman who had injected heroin (and later NPF) for nearly ten years, was a prime example. "I'm going to tell you this," she began "Suboxone *does not work* with fentanyl." Despite several successful past self-treatment episodes with buprenorphine, Gaia's most recent attempt was disastrous. Her boyfriend Jay related the story of their recent joint attempt at self-treatment:

> I was almost 72 hours into withdrawal…and I took it [Suboxone] and it made me… I couldn't believe it. Cuz I don't puke or get diarrhea, I don't have that happen ever…But immediately—Bam! Not even five minutes after I took it I was dripping sweat. It felt like water had just gotten dumped all over me, I'm puking and it's coming out every end.

Seeking alternatives

After experiencing precipitated withdrawal from attempts at self-treatment with buprenorphine, many participants changed their beliefs and practices surrounding self-treatment and treatment-seeking. Shane, a 46-year old with years of experience working as a counselor in drug treatment facilities, spoke of his recent instance of self-treatment modification:

> I got started [using NPF again] when I was playing music and I had been using for a while and wanted to get off so I had gotten some Subutex [buprenorphine] from a friend. I waited about 16 hours when I started feeling the withdrawal symptoms and took half of one and oh man. 15 minutes later I was in precipitated withdrawal. I couldn't sit still, I had really bad GI upset, was dry heaving… it was horrible.

Participants such as Jay and Gaia, however, were more definitively impacted by the reactions incurred by their attempts at treating their NPF use with non-prescribed buprenorphine. In response, they sought out new forms of treatment. Both decided to enroll in methadone-based treatment, where they have successfully transitioned off of heroin/NPF. Although Jay resented the daily dosing schedule mandated by the methadone clinic, he understood it to be his most viable option since, in his words, "Suboxone is not the answer to fentanyl." Gaia, his partner, elaborated:

> (Y)ou have to be clean four or five days before you can even take the Suboxone. So you're sick four or five days and it's like, it's not, no. It's like you can't do it…, I tried it a couple of times and I just couldn't do it. But methadone, methadone you can take, methadone works with the fentanyl. You can take methadone and you can, you know, you can take it and you're not gonna, it doesn't make you sicker, it makes you better. So, methadone is, does work with the fentanyl.

What Our Patients are Asking

COMMENTARY

A Plea From People Who Use Drugs to Clinicians: New Ways to Initiate Buprenorphine Are Urgently Needed in the Fentanyl Era

Kimberly L. Sue, MD, PhD, Shawn Cohen, MD, Jess Tilley, and Avi Yocheved

Journal of Addiction Medicine 16(4):p 389-391, 7/8 2022. | DOI: 10.1097/ADM.0000000000000952

Buprenorphine Initiation Strategies

- Collaborative Decision Making
- Low Dose Initiation
- High Dose Initiation

Buprenorphine Initiation Strategies

Strategy	Setting	Protocol	Pros	Cons
Standard Initiation	Level 1.7, 2.7, 3.7	Start at 4-8mg, titrate up to 32mg	Familiar Easier (no cutting of tabs/films)	Less effective in fentanyl era Difficult to be in withdrawal for long period of time, patients may give up
Low-dose Initiation	Level 1.7,2.7 NOT 3.7	Titrate up to 24mg +mg prn	Less intimidating than high dose Lower chance of precipitated w/d (in theory)	Complicated Takes a long time Hard to stick to “quit date”
High Dose Initiation	Level 1.7, 2.7, 3.7	Dose up to 32mg	Rapid Easier (one size tab only, simple process)	Can be intimidating to pts Hard to self-assess readiness Precipitated w/d can be severe if occurs
Low-High Dose Initiation	Level 3.7 (most likely)	Low dose for 24 hours, then high dose (up to 40mg)	Rapid Initial low dose decreases fear of high dose	Requires 2 different size tabs Requires tracking time and # of doses
Naloxone to High Dose Initiation	Level 1.7, 2.7	Self-administer naloxone, take 24 mg, increase to 32mg Day 2	VERY rapid (under an hour)	Requires high distress tolerance

Collaborative Decision-Making for Initiation

In selecting which initiation method, consider:

- Past experiences with withdrawal management/initiation
- Current life/living situation (unhoused is not necessarily an exclusion for outpatient withdrawal management)
- Motivation, distress tolerance, and overall patient goals (comfort, speed, privacy).

Reasons to consider inpatient withdrawal management:

- Concurrent regular use of alcohol or benzos
- Other medical/psychiatric co-morbidities, particularly if unstable or triggered by stress
- H/o severe precipitated withdrawal/severe anxiety about process
- Unhoused in high-risk setting and/or inappropriate housing situation (sole caregiver for children, etc)
- Overall low distress tolerance
- High use pattern with daily IV fentanyl use

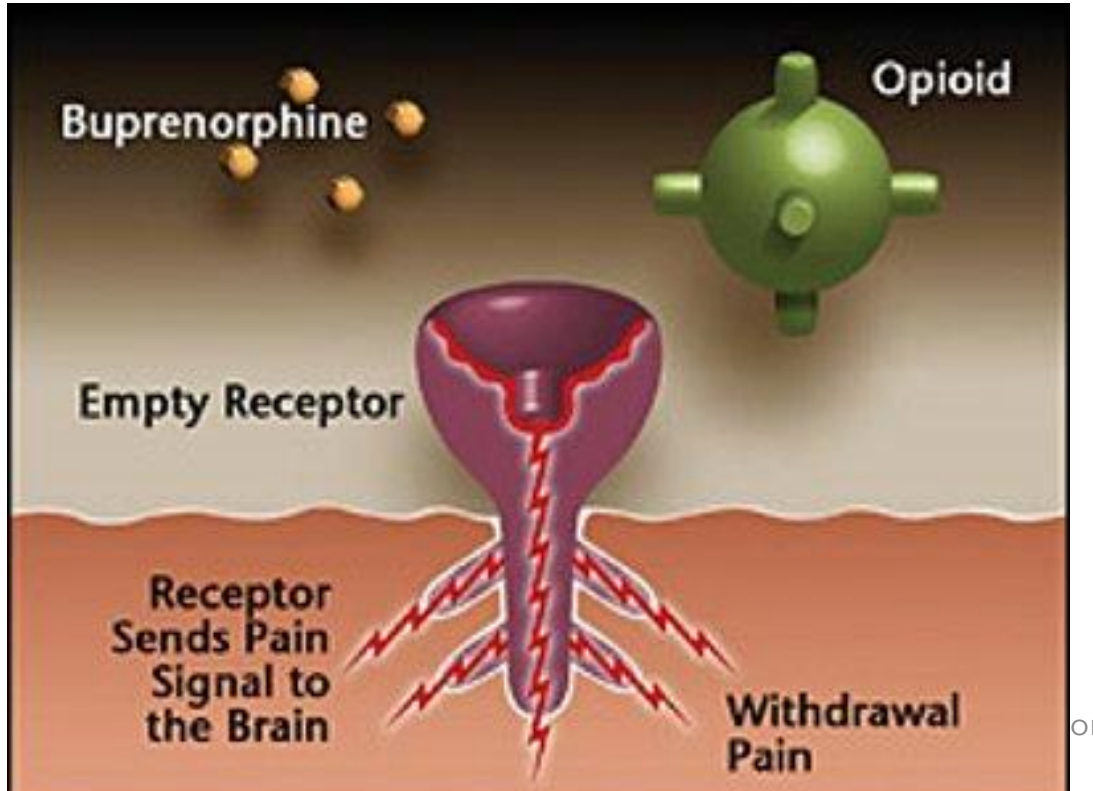
Three Basic Approaches to Starting Buprenorphine

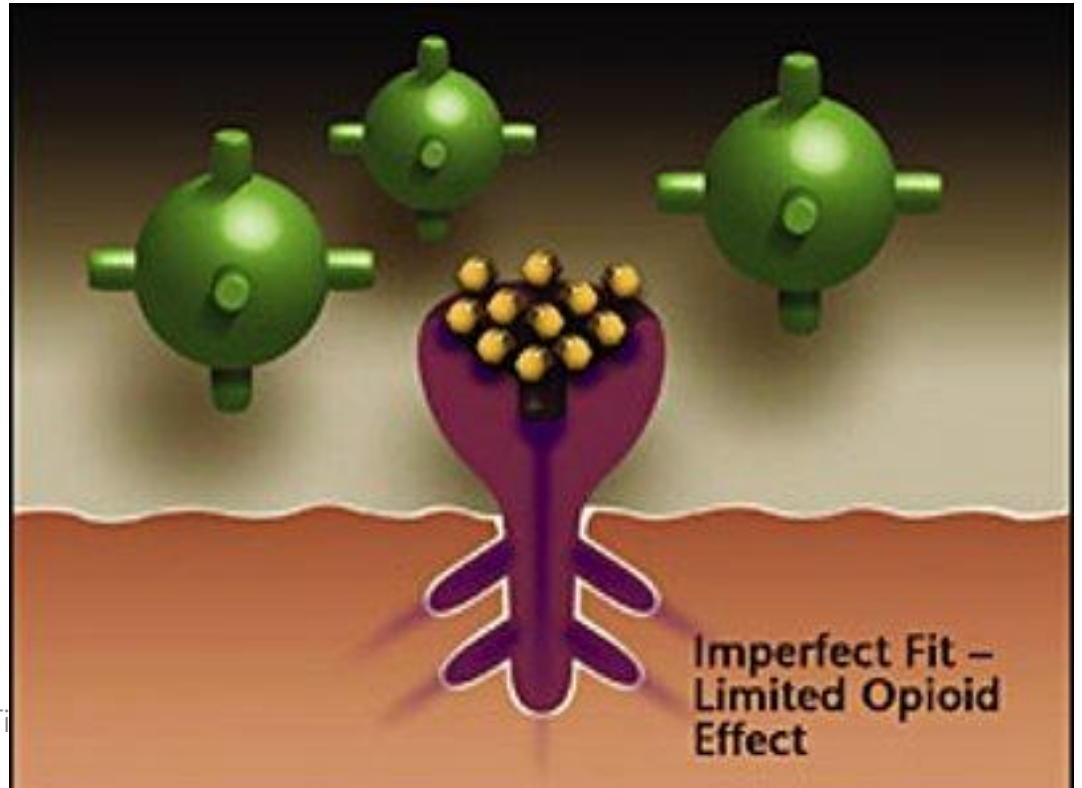
- Standard Initiation
- Low Dose (Micro) Initiation
- High Dose (Macro) Initiation

Standard Buprenorphine Induction

Requires period of abstinence (~24-72 hrs) from full opioid agonists – which translates to moderate opioid withdrawal

But, once buprenorphine is started… the more you give, the better you feel.

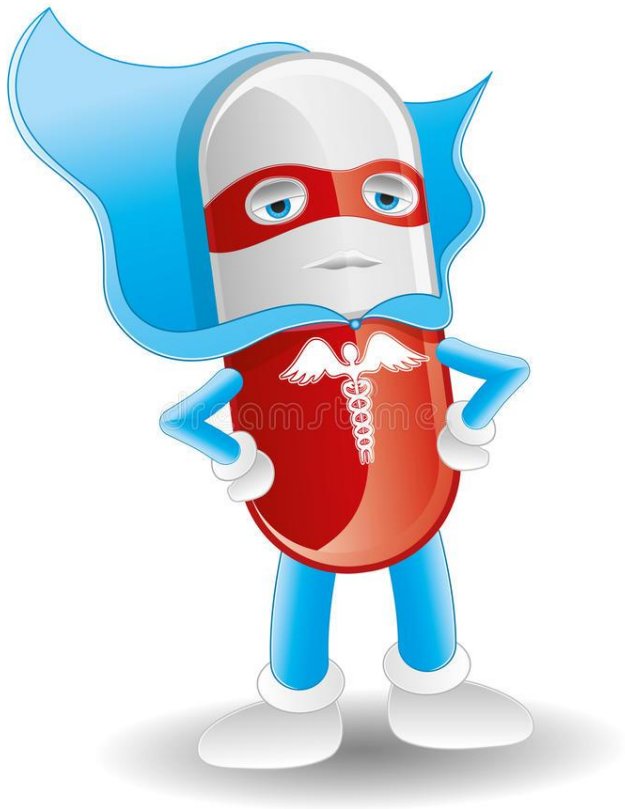




Barriers to Standard Buprenorphine Induction

- For people using fentanyl:
  - Unable to tolerate withdrawal symptoms for several days
  - Standard starting dose of 4mg places patient right in the middle of "PW Window"
- Some patients cannot or will not tolerate opioid withdrawal
  - Patients with chronic pain on long-term opioids
  - Difficult past experiences
  - Withdrawal is a strong trigger for opioid use
- When opioid withdrawal is contraindicated
- Transitions from long-acting opioids such as methadone - required to first reduce dose prior to induction
  - Dose reduction is below therapeutic levels, which can lead to opioid use disorder treatment destabilization and return to use
- Risk of precipitated withdrawal – past experience, vicarious experience, fear

Low-dose Initiation Benefits



- Based on the pharmacologic hypothesis that small amounts of buprenorphine should not precipitate withdrawal.

  Eliminates the need for patients to experience moderate opioid withdrawal as they continue on the full opioid agonists, including long-acting opioids, throughout the course of the induction

  Lower risk of precipitated opioid withdrawal with a low-dose initiation compared to a standard initiation

Low-dose Initiation Basics

- Buprenorphine is started at a very low dose **while the full opioid agonist is continued.**
- Buprenorphine is introduced onto the mu opioid receptors so slowly that minimal to no opioid withdrawal is experienced during the induction.
- The buprenorphine dose is gradually increased until it occupies a larger portion of the opioid receptors than the full opioid agonist, at which time the full opioid agonist is discontinued.
- Due to buprenorphine's long half-life and high binding affinity for mu opioid receptors, buprenorphine will accumulate over time and **slowly displace full mu agonists** from the opioid receptors.
- Some theories that low doses help to **"re-sensitize"** the mu opioid receptors

Low-dose Initiation Protocol Selection

- Multiple protocols exist
- Utilized in addiction medicine practices, primary care, hospital settings
- The first published report was in 2010 from Switzerland, termed the "Bernese Method"
- Subsequent multiple studies of inpatient protocols
- Our recommended PCHC protocol is adapted from published protocols and clinical experience

Bernese Method

Full Agonist Discontinued

Day	Total dose
1	0.25 mg
2	0.5 mg
3	1 mg
4	2 mg
5	4 mg
6	8 mg
7	12 mg

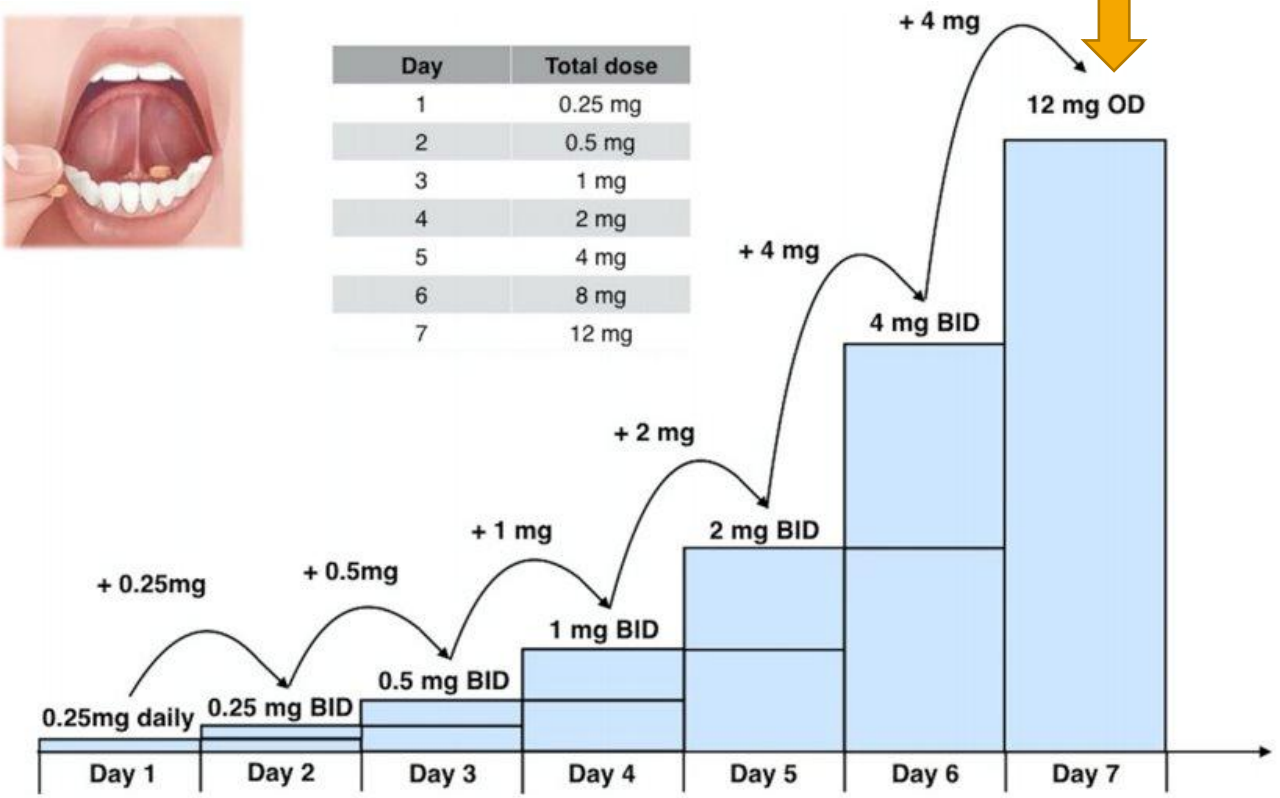


Fig. 1 Buprenorphine/naloxone microdosing regimen (daily witness ingestion). The team partnered with a local pharmacy who were able to split that tablets for microdosing. The tablet splitting may not have been 100% accurate, however it was effective for this patient, given that the technique is to start low and gradually increase and best practice for dosing has yet to be established

The Howard Street Method

ORIGINAL RESEARCH

The Howard Street Method: A Community Pharmacy-Led Low Dose Overlap Buprenorphine Initiation Protocol for Individuals Using Fentanyl

Marnie Noel, PharmD, BCPP, Elizabeth Abbs, MD, Leslie Suen, MD, MAS, Lysa Samuel, PA, Sarah Dobbins, MPH, PMHNP, PhD, Michelle Geier, PharmD, APh, BCPP, and Christine S. Soran, MD, MPH

FIGURE 1. Typical blister-pack schedule of BUP and BUP-NLX

Suggested LDI Protocol for Short-acting Opioids (excluding Fentanyl)

DAY	Daily Dose	Sig	Full opioid agonist
1	0.5 mg	0.5 mg qday	Continue
2	2 mg	1 mg twice a day	Continue
3	4 mg	2 mg twice a day	Continue
4	6 mg	2 mg three times a day	Continue
5	8 mg	4 mg twice a day	Taper or Continue
6	12 mg	4 mg three times a day	Taper or Continue
7	16 mg	8 mg twice a day	Discontinue

Suggested LDI Protocol for Long-Acting Opioids (e.g. Methadone ≤ 100mg)

DAY	Daily Dose	Sig	Full opioid agonist
1	0.5 mg	0.5 mg qday	Continue
2	0.5 mg	0.5 mg qday	Continue
3	2 mg	1mg BID	Continue
4	4 mg	2 mg BID	Continue
5	6 mg	2 mg TID	Continue
6	8 mg	4 mg BID	Continue
7	12 mg	4 mg TID	Continue
8	16 mg	8 mg BID	Discontinue

Suggested LDI Protocol for Fentanyl

DAY	Daily Dose	Sig	Full opioid agonist
1	0.5 mg	0.5 mg qday	Continue
2	1 mg	0.5 mg BID	Continue
3	1.5 mg	0.5mg in AM, 1mg in PM	Continue
4	4 mg	2 mg BID	Continue
5	6 mg	2 mg TID	Continue
6	8 mg	4 mg BID	Continue
7	12 mg	4 mg TID	Continue
8	16 mg	8 mg BID or TID	Discontinue

Patient Counseling for Low-Dose Initiation

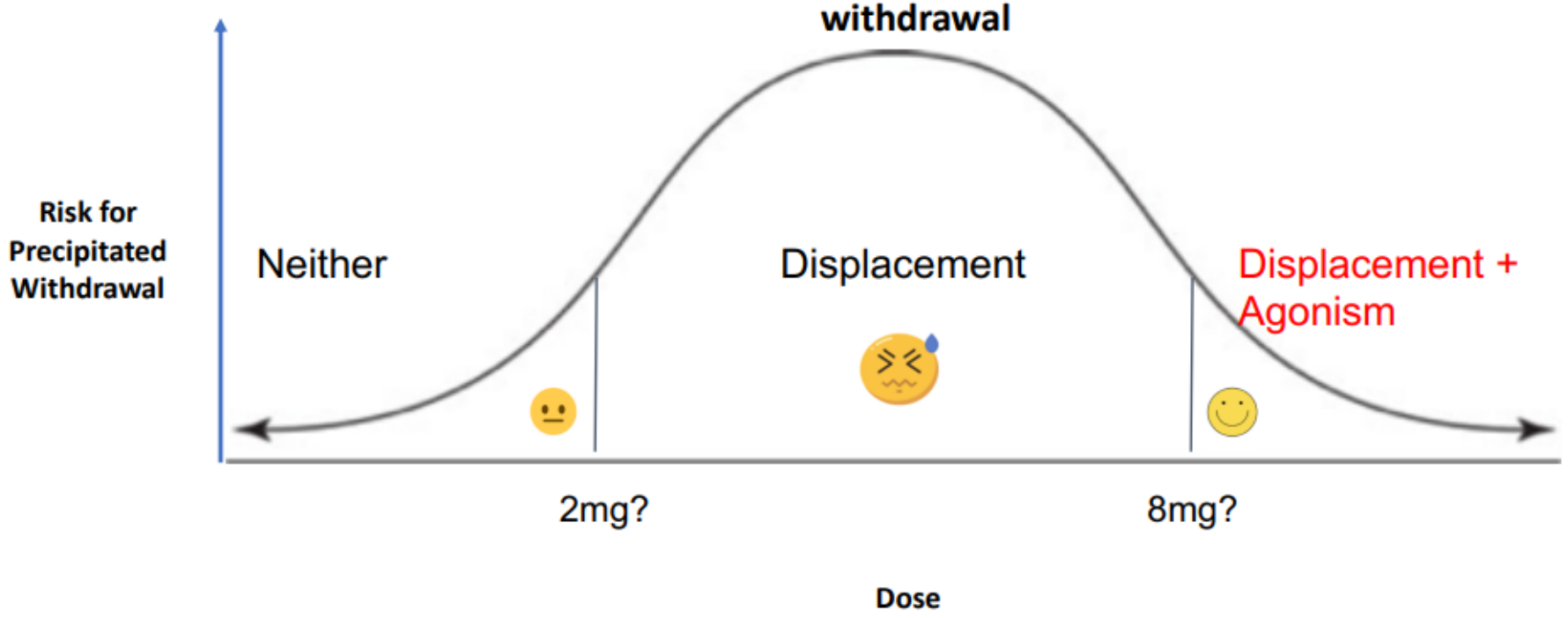
- Adverse effects tend to be mild and include: insomnia, restlessness, irritability
- Consider Rx for adjunctive medications for potential withdrawal symptoms (start around day 3-4):
  - Clonidine, hydroxyzine, loperamide, ondansetron, tizanidine, methocarbamol
- Precipitated opioid withdrawal is not a significant risk if protocol followed, but should counsel patient that this is a risk if they take more buprenorphine than what is prescribed
- Use films for easy of cutting into quarters
- Reminder: prescribe Naloxone and counsel on use
- Follow-up: Day 3 or 4 AND Day 7 or 8
- Okay to increase dose beyond 16mg on Day 8 and beyond
- If transitioning from methadone, be sure to coordinate care with OTP in advance

High Dose Initiation – The Why

- Gets buprenorphine onto receptors quickly without the need for extended, complicated initiation
- Provides higher doses of medication needed in the setting of fentanyl
- Originated in Emergency Department settings to maximize opportunities for medication starts after naloxone administration – expanded to patients presenting in withdrawal

High Dose Buprenorphine Initiation – How It Works

Rationale: Avoids the significant withdrawal needed to start buprenorphine traditionally by speeding up induction and reduces risk of precipitated withdrawal



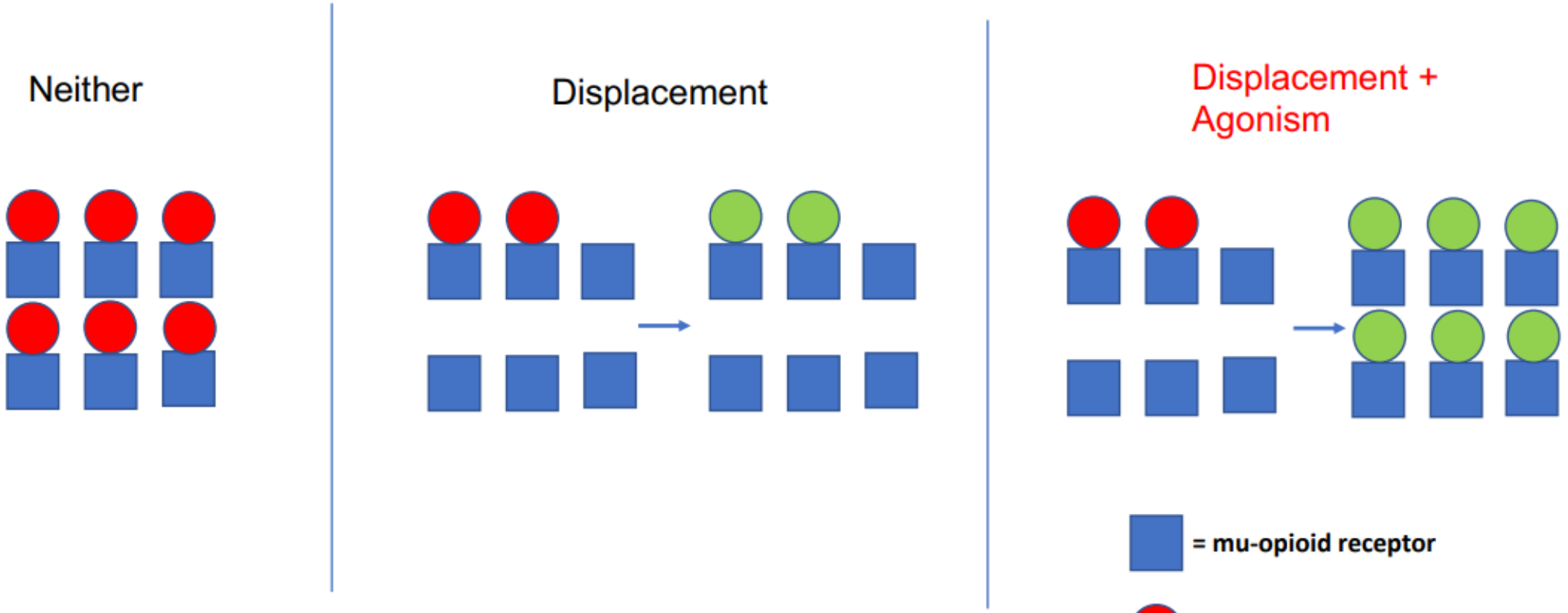
Herring AA, et al. *Am J Emerg Med.* 2019 Dec;37(12):2259-62.
Huhn AS, et al. *Drug Alcohol Depend.* 2020 Jul 2;214:108147.

RUTGERS New Jersey Medical School

State of New Jersey DHS Department of Human Services

RUTGERS Project ECHO

High Dose Buprenorphine Initiation



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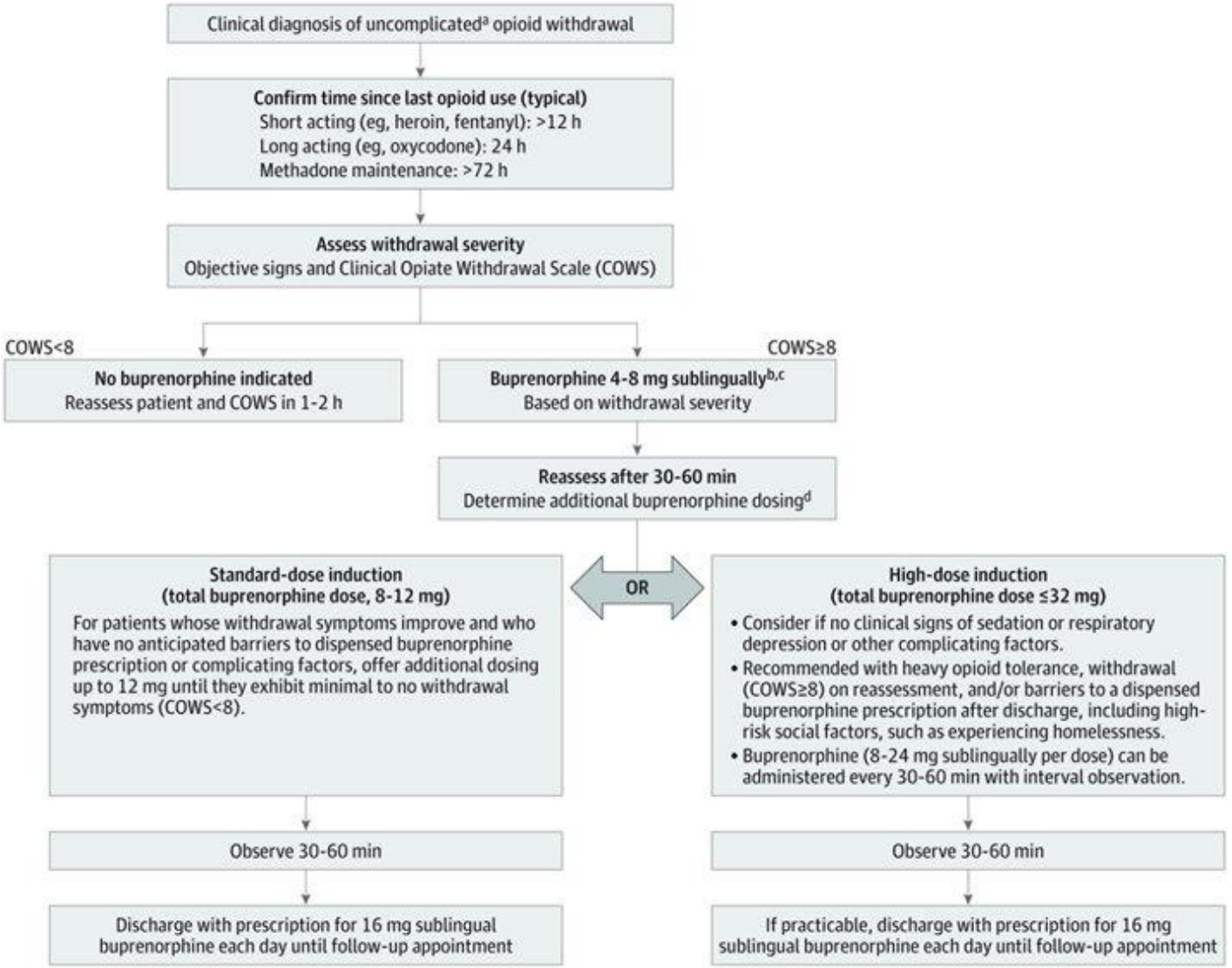
State of New Jersey DHS Department of Human Services

RUTGERS Project ECHO

Strategies for High-Dose Initiation – High Dose ED Start



- Timing: at least 12 hours after last use
- COWS: not that high! (8)
- "test dose" and then a higher dose
- Dosing up to 32 mg for someone who won't have follow up: **key strategy for overdose prevention**

Strategies for High Dose Initiation – At Home/In Office

When to start buprenorphine:

- Wait at least 48 hours from last use

-- OR–

- COWS ≥16 or SOWS ≥ 21

-- AND --

- At least 2 objective signs of withdrawal (dilated pupils, tearing, rhinorrhea, gooseflesh you can feel)

Adjuncts Before/During/After Starting Buprenorphine:

- Gabapentin 300-600mg TID
- Clonidine 0.1-0.2 mg TID
- Ondansetron 4-8mg TID
- Tizanidine 2-4mg QID

-- OR –

- Methocarbamol 1000mg TID

How to take buprenorphine:

- Start with 8-16mg all at once (I strongly advise 16mg)
- Wait an hour. If needed, take another 8mg
- Wait another hour. If needed, take another 8mg.
- Max dose on Day 1: 32mg
- Day 2: start with 8-16mg in AM. Titrate up to daily dose of 24mg

Name: _____

DOB: _____

IT MATTTRs 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

When people feel worse after a dose, what is going on?

DDX for within 1-2 hours of buprenorphine dosing:

- Displacement without agonism (precipitated withdrawal)
- Undertreatment of withdrawal

DDX for several hours after buprenorphine dosing:

- Mobilization of more fentanyl from tissues to bloodstream and mismatch between buprenorphine in system and fentanyl in system- -- the “Cage Fight”

Treatment: More Buprenorphine

Patient Counseling for High-Dose Initiation

- Prepare for discomfort
- It's best (but not necessary) to have someone there who can help you:
  - Hot shower/bath with essential oils
  - Massage
  - Hydration, easy foods
  - Help administer meds and follow instructions
  - Coordinate care with provider
- I generally call the patient every day during high-dose initiation, follow- up in person 5 days
- Do NOT:
  - Take 4mg as a starting dose
  - Rely solely on COWS/SOWS for initiation threshold

Know Your Adjuncts! Especially For High-Dose Initiation

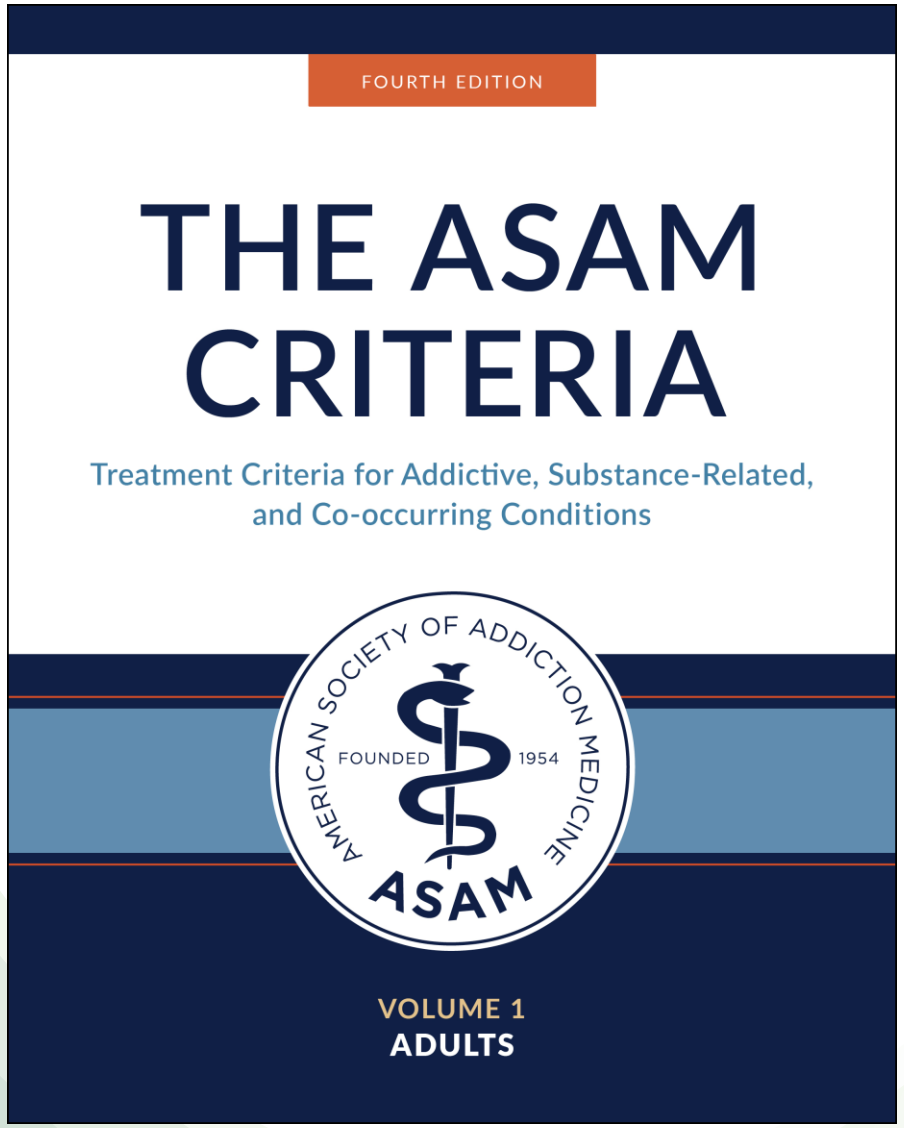
Use of adjunct medications is particularly important for severe restlessness and anxiety associated with withdrawal from fentanyl, *even after maintenance dose of buprenorphine is achieved.*

Symptom	Medications and Dosing	Notes
Muscle Spasms/ Dystonia	Tizanidine 2-4 mg QID Methocarbamol 1000mg -1500 mg TID	
Nausea	Ondansetron starting dose at 8mg (4mg less effective with fentanyl) Judicious use of promethazine; monitor for over-sedation	Nausea can be particularly severe in patients with IV fentanyl use
Anxiety	Clonidine up to 0.3mg QID Diphenhydramine	Anecdotally, diphenhydramine tends to work better than hydroxyzine in fentanyl withdrawal
Restlessness/agitation:	Gabapentin up to 900mg TID Olanzapine 5mg BID or TID	Use high doses of gabapentin in first 3 days, then taper or stop
Pain	Ibuprofen 800mg QID APAP 1000mg QID	Higher doses for only a short period of time; consider contra-indications (NSAIDs: cardiovascular disease, renal failure, gastric ulcer; Acetaminophen: active AUD and liver disease)
Sleep	Trazodone 100mg qhs Quetiapine 50-100mg Mirtazapine 15mg	Try quetiapine or mirtazapine if trazodone ineffective

When To Start Talking About What Happens After Initiation

As soon as possible!

- All patients should be offered psychosocial treatment, which may include psychotherapy, SUD counseling and psychoeducation to address SUD and co-occurring mental health
- Options include 1:1 counseling, group therapy, peer support, meetings
- Consult your local recovery center
- Per ASAM guidelines, a treatment planning assessment should be conducted or reviewed within the first three visits
- Do not withhold medical treatment if patient declines BH treatment



Tools & Supports you can develop for your practice…

- Quicktexts for Rx Sig and Patient Instructions
- Patient handout
- Integration with Walk-in Care
- Review Buprenorphine Consent/Treatment agreement to see if any changes/updates are necessary
- Integration of RN/Pharm D into bupe initiation and monitoring
- Any other ideas?

Case #1

- 67 yo male with h/o rectal carcinoma, alcohol use disorder, opioid use disorder
- OUD treated on 97mg methadone
- Drinks a pint of Fireball daily, sometimes 2 or 3
- Lives with roommates in rural area
- Supports include his case manager and his cat
- Loves to paint, mostly pastoral scenes of Maine
- Wants to get off methadone and onto buprenorphine, as he is exhausted from the 2-hour round trip to the OTP daily
- UDS + for methadone, EtG
- Lean, mildly irritable

Case #2

- 23 yo male with h/o OUD, no other medical history
- Released from jail 3 months ago. While incarcerated, was on bup/naloxone 8mg. “It helped in jail, but not on the outside”
- Since release, has had return to use: 1-1.5 grams fentanyl daily, injected
- No history of overdose
- Lives with significant other in rented room
- Works as a furniture mover
- Feels he needs to keep working, cannot miss a day as he is new at this job
- UDS + for cocaine, fentanyl. Exam unremarkable except for poor dentition

Case #3

- 35yo female with history of bipolar d/o, OUD comes in with her husband
- Using for past 2 months, “anything we can get our hands on”
- Cannot quantify amount of fentanyl use. States “a lot”: multiple times per day, smoked
- Tried suboxone once, took 4mg which made her sick. Took another 4mg, which made her sicker
- Was outdoors, now staying with mother-in-law, who has custody of her daughter
- UDS: + methamphetamine, + fentanyl
- Very soft-spoken, disheveled, sores on face and arms

Thank you!

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