ECHO IDAHO:
Opioids, Pain & Substance Use Disorders

Using Low Dose Inductions To Convert Patients From Methadone and Other Full Agonist Opioids To Buprenorphine

10/10/2024

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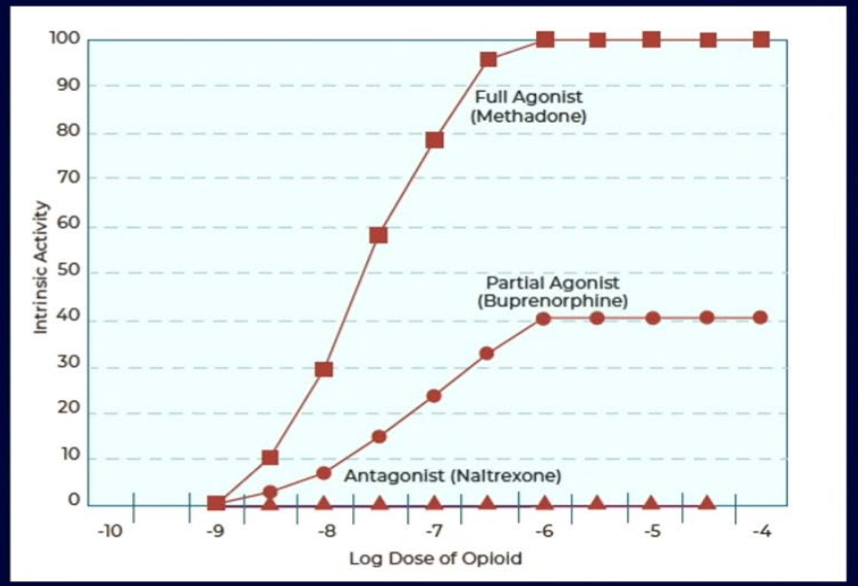
Learning Objectives

- 1) Understand the general concepts of low dose inductions
- 2) Be familiar with different low dose inductions regimens
- 3) Be familiar with the possible advantages and disadvantages of low dose inductions
- 4) Be familiar with the unique situations with Fentanyl

Buprenorphine: KEY characteristics

High Affinity



Partial Agonist

Volpe, *Regul Toxicol Pharmacol* 2011
SAMHSA, *TIP 63, 2020*

Issues with converting to Buprenorphine

- Replacing methadone, which is a full agonist, with Buprenorphine, a partial agonist with higher receptor affinity, will knock methadone off of the receptor and precipitate sudden withdrawal.
- Some risk factors for this are high Methadone dose, short time to conversion, and female gender

Can take as much as 96 hours off of Methadone to get to a level of where this does not happen.

We can do this gradually with low dosing and "bridging"

- This consists of starting off with very low doses of Buprenorphine with gradual increases and allowing it to take over the Mu receptors.
- Eliminate patients having to go through withdrawal.
- Can help prevent an increase in pain during the induction phase.
- Can be done with much higher doses of Methadone. Typically, we like to get patients down to 30 or maybe 40 before doing typical induction.

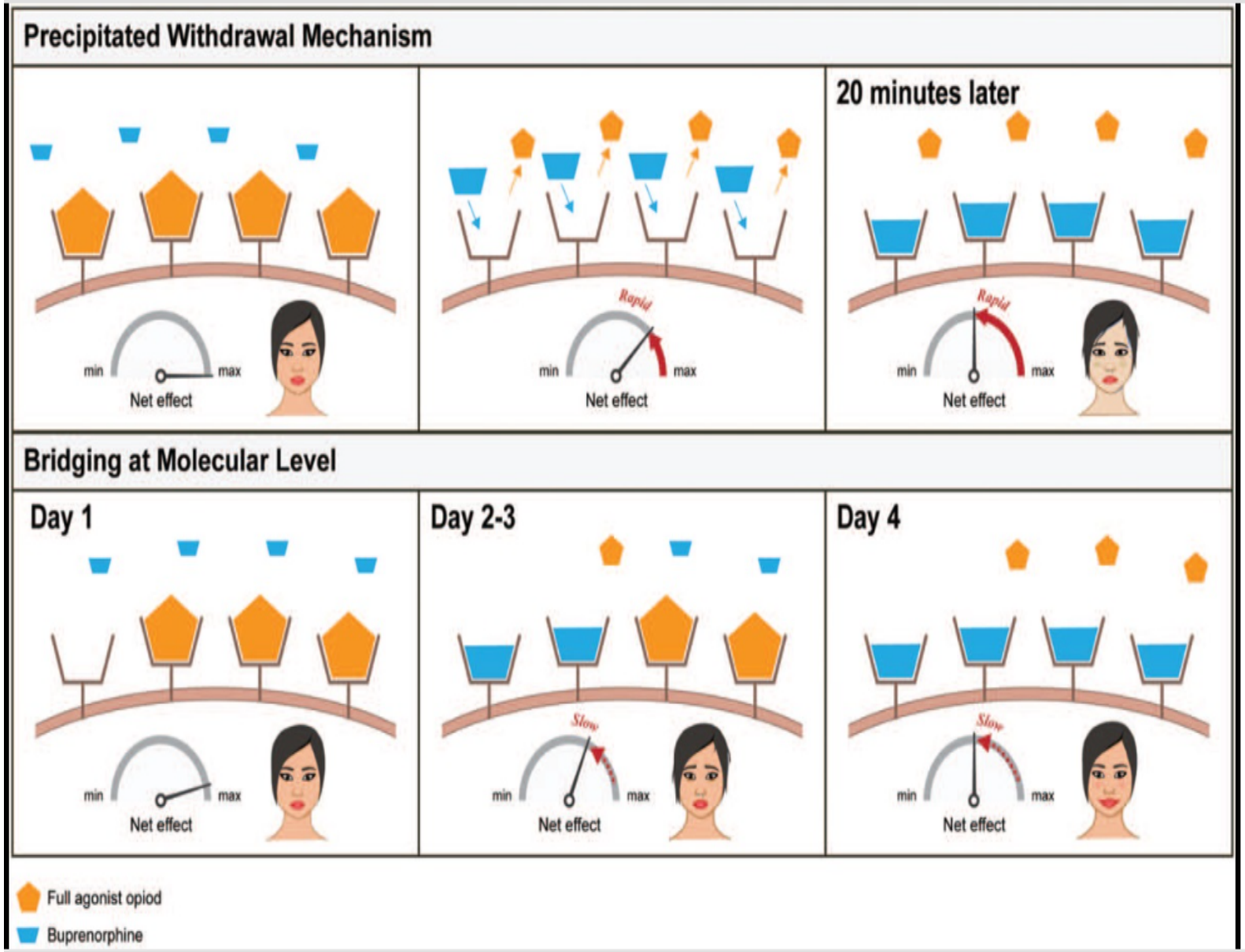


FIGURE 1

Mechanism behind precipitated withdrawal mechanism as well as bridging: Partial agonist opioid with high affinity for μ-receptors replaces the full opioid agonist rapidly over a short period of time causing a massive change in the net μ-receptor activation leading to rapid precipitated withdrawal. This can be mitigated by bridging, where the gradual introduction of higher affinity partial agonist opioids can help minimize withdrawal symptoms.

Source

A Review of Novel Methods To Support The Transition From Methadone and Other Full Agonist

Let’s look at different induction methods

- What we’ve typically done:
  - Taper Methadone dose to 30 mg or less (or maybe 40)
  - 36-72 hours off of methadone with patient presenting in withdrawal
  - Start induction with small doses of Buprenorphine and titrate upwards to alleviate withdrawal symptoms and/or pain.
    - Typically, this involves 4 mg of Buprenorphine with a repeat of 4 mg on day 1. Fentanyl situation can be different.
    - Day 2 this might be 8 plus 4 plus 4, with further titration up on subsequent days if needed.
  - Works best for methadone doses less than 40 and least well if over 60.
  - Surprisingly, there was a trend for more successful transfer completion when buprenorphine was given in first 24 hours when only mild withdrawal and better transfer when starting doses were less than 4mg.
  - Tapering people down to 30 is a dangerous time where bad things can happen and 30 sub therapeutic.

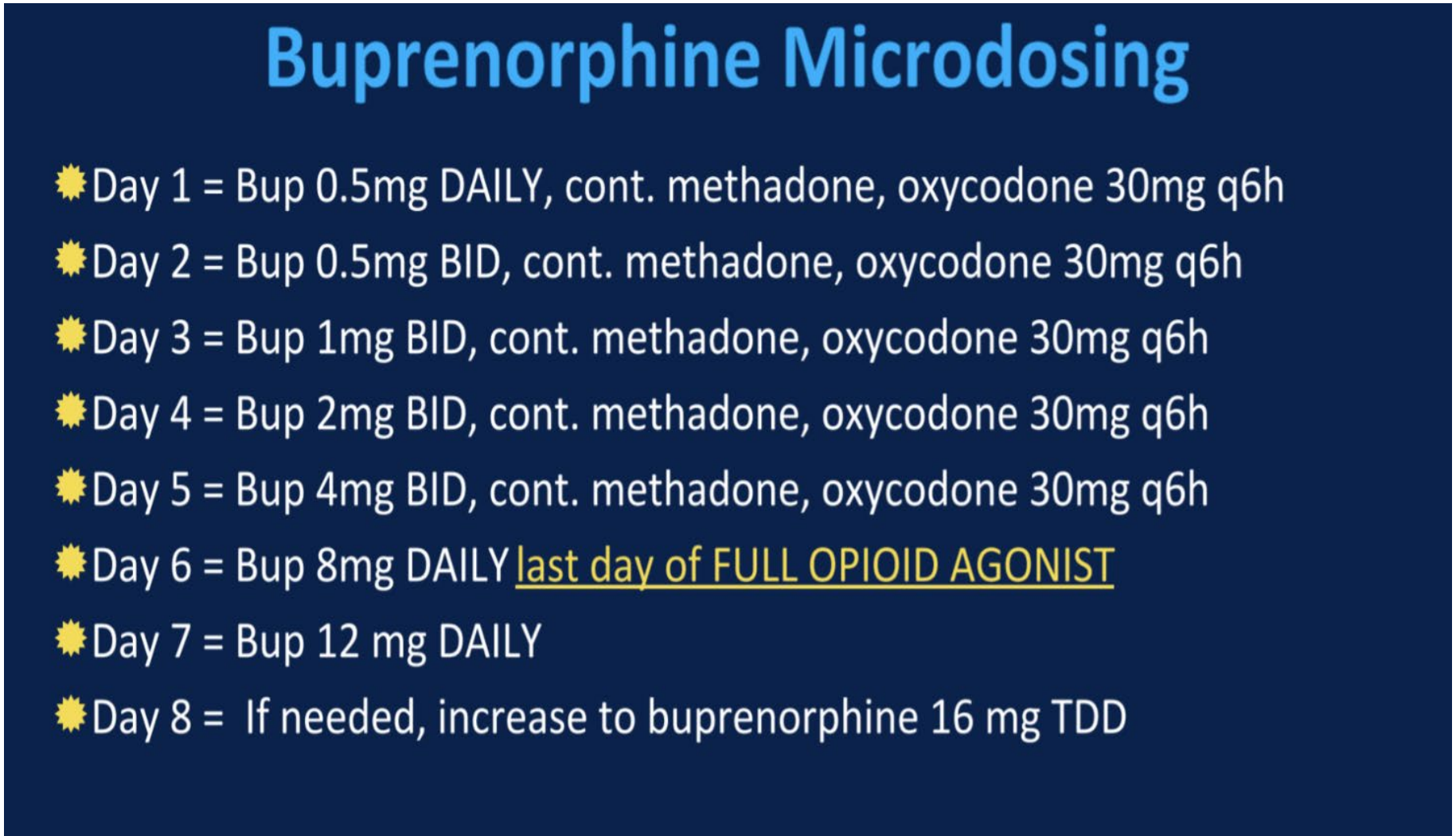
Different ways to use low doses during an induction.

- There are many regimens out there now-not widely validated yet, but the principles are all the same. Buprenorphine gradually takes over the Mu receptors and eventually saturates them with little or none of the original opioid being bound.
- Best to leave on the full dose of full mu agonist while going up on the Bup, and then stop on the last day.

Bernese Method and methods that led to it

- Divide up Buprenorphine pills into eights or quarters and do slow titration. Like starting with .2 mg q 6 hours.
- An example of a regimen would be:
  - Day 1: ¼ of 2 mg pill (.5mg)
  - Day 2: ¼ of 2 mg pill (.5mg) bid
  - Day 3: ½ of 2 mg pill (1mg) bid
  - Day 4: 1, 2 mg pill bid
  - Day 5: 2 of the 2 mg pill (4mg) bid
  - Day 6: 2 of the 2 mg pill (4 mg) tid
  - Day 7: 8 mg bid and stop the full agonist Or you might do this after day 6 at 12 mg and titrate up to 16 later as needed.
  - Can pause for a day or 2 along the way if withdrawal symptoms occur and give body change to equilibrate.

Another very similar one I've used, although I would continue the full agonist up through day 7



More tips

- You want people on a predictable dose of their full agonist before doing this. Like if they are having acute pain after surgery and dose of full agonist varies, not a good time.
- Don’t forget about adjunctive meds for withdrawal if you need them, but hopefully won’t, e.g., Clonidine, Ibuprofen, Loperamide
- You can pause the induction and keep same doses going for more than one day.

Slightly different, same principle. 12 given on day 7.

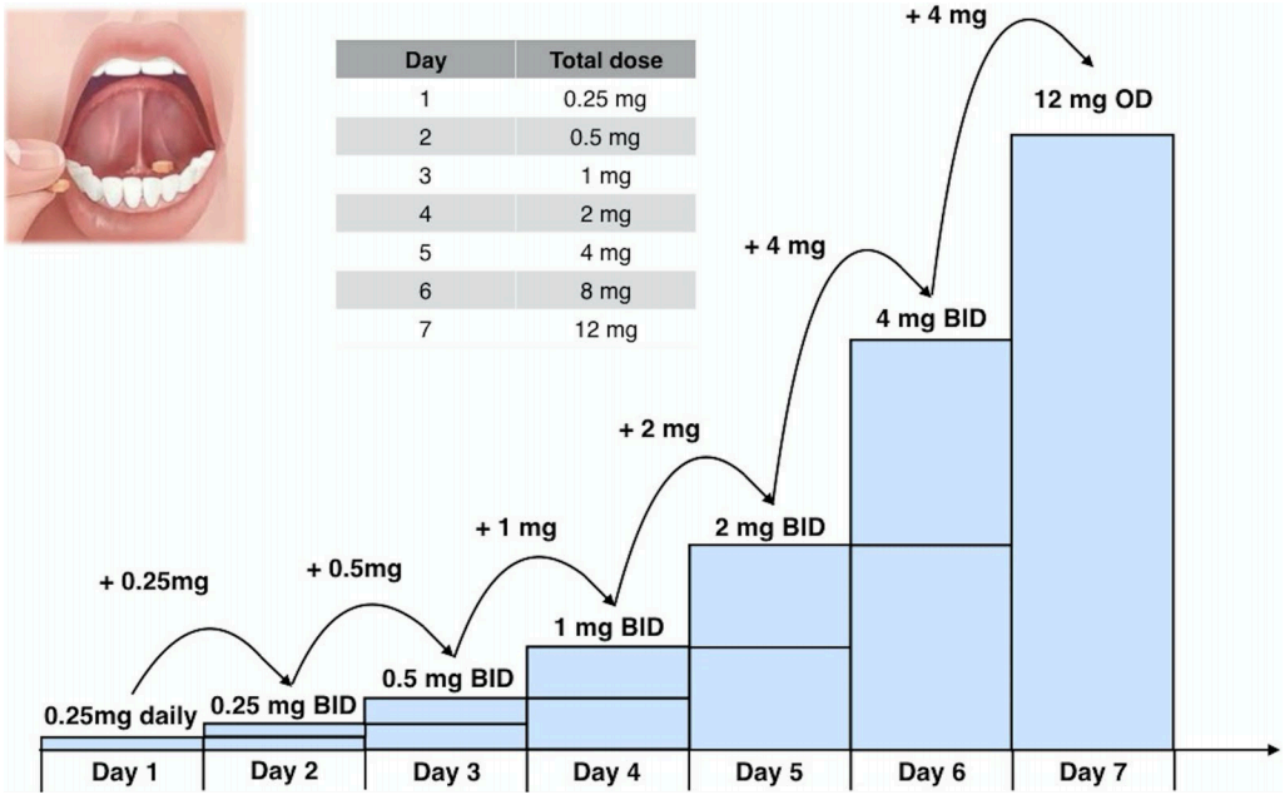
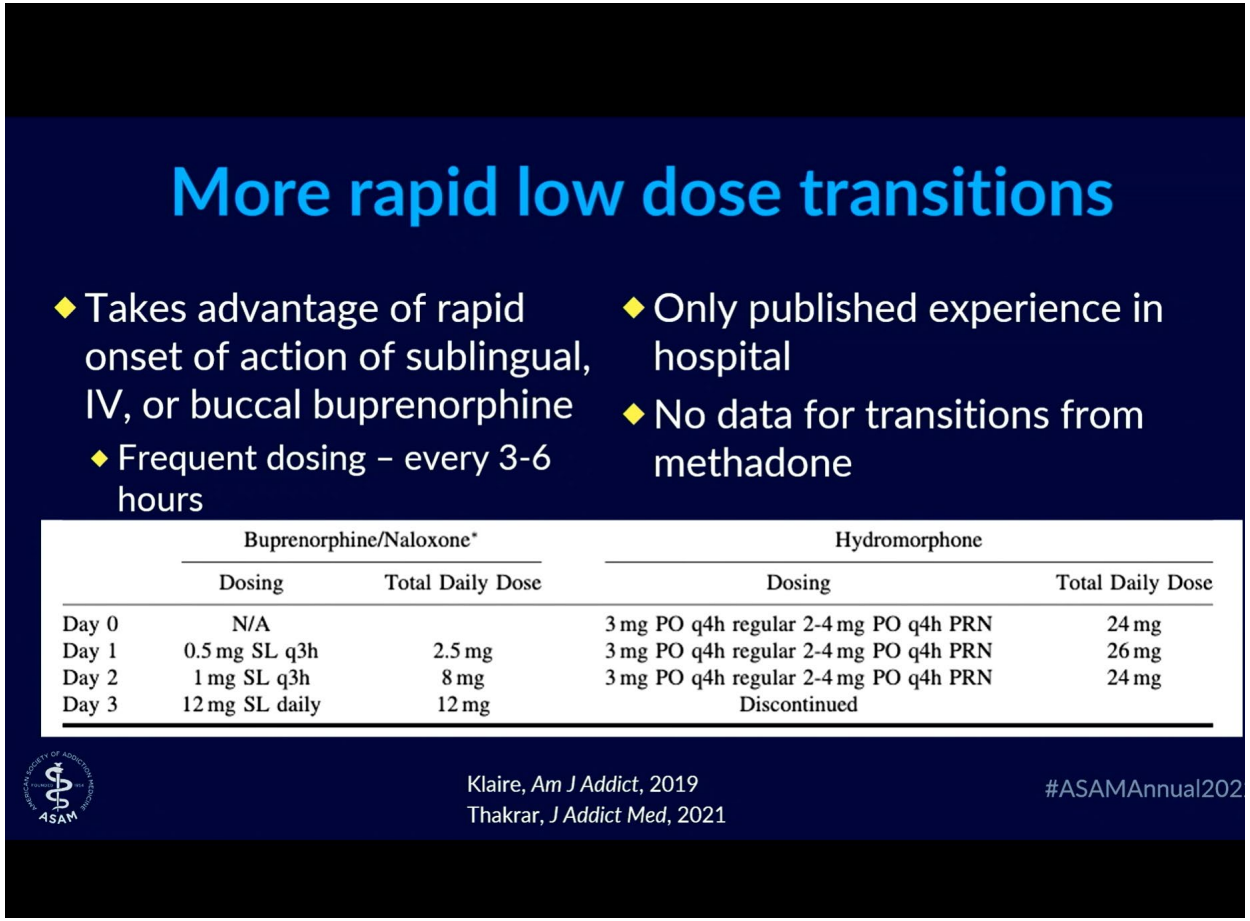


Fig. 1 Buprenorphine/naloxone microdosing regimen (daily witness ingestion). The team partnered with a local pharmacy who were able to split that tablets for microdosing. The tablet splitting may not have been 100% accurate, however it was effective for this patient, given that the technique is to start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

Or a more rapid induction which you might consider for hospitalized patient.

- .5 mg Bup q 3 hours on day 1
- 1 mg q 3 hours on day 2
- 12 mg consolidated dose on day 3 with additional 2 mg prn.



Or over 24 hours (not totally sure about this)

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Day 1 time in hours from start of induction	Buprenorphine/Naloxone SL dosing (mg)	Cumulated total dose of buprenorphine over 24 hours	Methadone dose
1	0.5	0.5	50 mg
2	0.75	1.25	–
3	1	2.25	–
4	1	3.25	–
5	1	4.25	–
6	1	5.25	–
7	1	6.25	–
8	1	7.25	–
Day 2	12 and 1–2 mg q3h PRN	12 mg + additional doses	STOP all methadone

SL = sublingual.

24-Hour Rapid Microinduction Dosing Schedule For Buprenorphine/Naloxone SL Using 50 mg of Methadone

But it can be difficult to break the pills-this is where the transdermal patch or buccal form can help.

- Peak plasma volume from patches occurs at 48 hours.
- Patch 20 mcg = 0.5mg SL daily
- Cost significantly limits this approach

Literature guide

Buprenorphine Formulation	Starting dose	Sublingual equivalent	Advantages	Disadvantages	Reference
Sublingual film	0.5mg	0.5mg	Simplest Allows frequent dosing	Hospitals may restrict splitting	Terasaki et al
Buccal film	225mcg	0.5mg	Rapid onset(~4hrs) Allows frequent dosing	Inpatient only (for OUD)	Weimer et al
Intravenous	0.15mg	0.5mg	Rapid onset Allows frequent dosing	Inpatient only	Thakrar et al
Transdermal patch	20mcg	0.5mg	Gradual onset	Expensive Inpatient only (for OUD)	Ghosh et al

Weimer, *J Addict Med*, 2021 Thakrar, *J Addict Med*, 2021 Ghosh, *CMAJ*, 2019
Hickey, *Med Clin North Am*, 2022 Terasaki, *Pharmacotherapy*, 2019

Sample Transdermal regimen

- Day 1: Place 20 mcg bup transdermal patch
- Continue both long and short-acting opioids
- For short-acting, can start SL bup/nlx at 24 hours; for long-acting, wait 48 hours. But do you really need to wait?
- Begin SL dosing with 1 mg BID (1/2 tab).
- Day 2: 1 mg BID
- Day 3: 2 mg BID
- Day 4: 4 mg BID.
- Day 5: 6 mg BID
- Day 6: 8 mg BID Stop full Mu agonist.
- Stop patch a couple of days into it.
- I am assuming that you can do the same sort of regimen with the Buccal preparation (225 mcg) for day one or longer, if need to.

Fastest protocol: Lembke & Raheemullah in JAMA March 2019

- Day 1, place 20 mcg bup patch for 24 hours
- Day 2, give 2 mg SL bup/nlx + 2-4 mg prn doses q 2-4 hours for maximum dose of 8 mg.
- Day 3, + 2-4 mg prn doses q 2-4 hours for max dose of 16 mg.
- Remove patch after 48 hours (after day 2). Discontinue full agonists by end of day 3.

Sample Buccal Regimen. Looks like this one would work especially well for someone who is also having pain because of the frequent dosing.

- 150 mcg every 6 hours on day 1
- 450 mcg every 6 hours on day two
- 1 mg sublingually every 6 hours on day 3
- 2 mg sublingually every 6 hours on day 4 then they stay with 8 mg
- Once the patient is on 8 mg you can try to take off the full mu agonist or leave it on temporarily if they need it for pain.

Fentanyl

- Very lipophilic and renally cleared. Can seep out of tissues for a while. Can have withdrawal even days after last took.
- How do you do low dose induction with someone using illicit Fentanyl on the street? It’s controversial.
- Can convert to stable dose of Methadone and then do low dose induction, but we can't do that outside of an OTP (opioid treatment program, ie. methadone clinic).
- If they are having pain, might consider converting to other full mu agonist like MS contin and then do low dose induction. But, can be risky and you have to have to have reliable patient and good communication with them and any family and friends. You don’t want them mixing the MS Contin and fentanyl.
- What if can’t do either. Then shared decision making, but I wouldn’t document that you recommended that they continue to use illicit fentanyl. They are choosing to do that after discussing options, but go over safe use: safe needle use, Narcan, never use alone and give “never use alone” hotline number (see slide at end of presentation), test small batches. If going this way, they need to use same exact dose and form that they were getting before on the street.
- Consider quicker induction, like 3 or 5 days.
- More support the better. May need to admit to hospital.

3-day rule

- The way things had been: One day's medication may be administered to the person or for the person's use at one time**.** Such emergency treatment may be carried out for not more than **three days** and may not be renewed or extended.
- Now practitioners who wish to dispense the full three days-worth of medication to patients at one time can make a request to DEA to receive permission to do so. You have to actually email the DEA to obtain the approval. Requests for exception must be emailed to: ODLP@dea.gov under the subject line: “Request for Exception to Limitations on Dispensing for OUD.”
- You can do a rapid low dose induction during this three days.
- If the patient is in the hospital, you can continue to give opioids for OUD as long as they are there.

Tips to succeed

- Daily phone calls
- Dosing guides.
- Set up pill box
- Help from pharmacy, including blister packs
- If patient on over 100 of methadone, go really slowly.
- Have good communication with OTP (Methadone clinic)

Conclusion, pros and cons.

- Can avoid significant withdrawal
- Can avoid significant pain
- Might be more acceptable to patients, especially ones who have failed typical inductions.
- Works better with patients on higher doses of methadone
- Better for synthetic opioids with unpredictable clearance.
- But regimens can seem complicated.
- Can take longer than typical induction.

Shared Decision making tool

Clinician instructions: use with patients who are eligible for low-dose induction based on length of hospitalization

Choosing How to Start Buprenorphine

We want to make it as comfortable as possible for you to start buprenorphine.

Buprenorphine (also known as Suboxone or Subutex) is a long-acting opioid and one of three medications used to treat opioid addiction. It reduces the use of other opioids and lowers the risk of overdose. We recommend it if you if you have cravings for opioids, if you are struggling to cut back on use, and if you have withdrawal when you stop opioids.

1. What is the issue? If you start the standard dose of buprenorphine while you have other opioids like heroin, fentanyl, or oxycodone in your system, it can put you into immediate withdrawal or make withdrawal worse. We call this "precipitated withdrawal."

2. Why does this matter? You may need opioids for pain OR you may have recently taken another opioid, like fentanyl or methadone, that lasts more than a few hours. It can be hard to stop opioids for many hours or days, especially in the hospital.

3. Have you started buprenorphine before? What did you do that time?

_____

4. What did you like about it and what did you not like about it?

_____

5. What is most important to you? You can check off more than one.

- ○ Continuing my opioid medications (either methadone or opioids for pain)
- ○ Managing pain
- ○ A fast transition to buprenorphine
- ○ Avoiding withdrawal
- ○ Using an approach with the most evidence
- ○ Starting buprenorphine the way I've done it before
- ○ Trying something new
- ○ Other: _____

6. Here are two options to start your buprenorphine:

	What it means:	*Reasons to choose:*	*Reasons NOT to choose:*
Standard start	• We stop all opioids and wait 8-72 hours for the opioids to wash out of your body before starting buprenorphine • We keep you comfortable with non-opioid medications	• More evidence • Sometimes faster	• Need to stop opioids and wait for withdrawal • Could worsen withdrawal
Low-dose, overlapping start	• We continue methadone or opioids for pain • At the same time, we start buprenorphine at a low dose and slowly increase the dose over a few days • Once buprenorphine is built up in your body, we stop other opioids • In our experience, this will not cause withdrawal	• Designed to minimize withdrawal • You continue methadone or opioids for pain at the same time	• Less evidence • Might cause withdrawal, especially if we don't follow the process • Sometimes slower and might mean you stay in the hospital for longer

No matter what you choose, we will monitor you and we can change course if needed.

7. What did we decide today?

- ○ Standard start
- ○ Low dose start
- ○ Continue to discuss and decide later

8. What are the next steps?

_____

Credit to Ashish Thakrar MD for creation, presented at AMERSA 2021

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