Low Dose Buprenorphine Initiation Strategies

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Disclosure Information

- Presenter 1: Melissa Weimer, DO, MCR, DFASAM
  - Presenter 3 Commercial Interests: Path CCM, Stock Options; CVS Health, Advisor

Learning Objectives

- Describe low dose buprenorphine initiation with opioid continuation and clinical indications for its use
- Discuss the rationale and potential risks and benefits of novel buprenorphine initiation strategies.

Resources/Pre-reading

JAM Narrative Review and Practical Guide

1 Page Outpatient Guide

Shared Decision Making tool

A minute on terminology: "LOW-DOSE" vs "MICRO-DOSE"

- Accuracy & connotation of terms are important, especially as we grow as a field
- In pharmacology and translational science, "micro-dose" refers to non-medical use
  - Connotation with LSD use
- We prefer "Low dose," "ultra low dose," or "Bernese method"
- If you can't shake "micro," we recommend "micro-induction"

Weimer, Fiellin. Addiction, January 2022.

Background

- In the United States Buprenorphine initiation guidance was codified in SAMHSA TIP #40 (c. 2004)
- Since then, the scope of OUD has increased dramatically
- Buprenorphine initiation much more widespread
  - Though still devastatingly limited
- There is now renewed interest in variations on the traditional buprenorphine initiation plan

2023 vs 2000

- Fentanyl and its analogues now ubiquitous
- Stimulant co-use increasing common and as high as 90% in some populations
- Additional synthetics such as xylazine are common in some regions.
- Diverse population with OUD—rural, urban, race/ethnicity
- Homeless and other social determinants substantially more common

Difficult situations

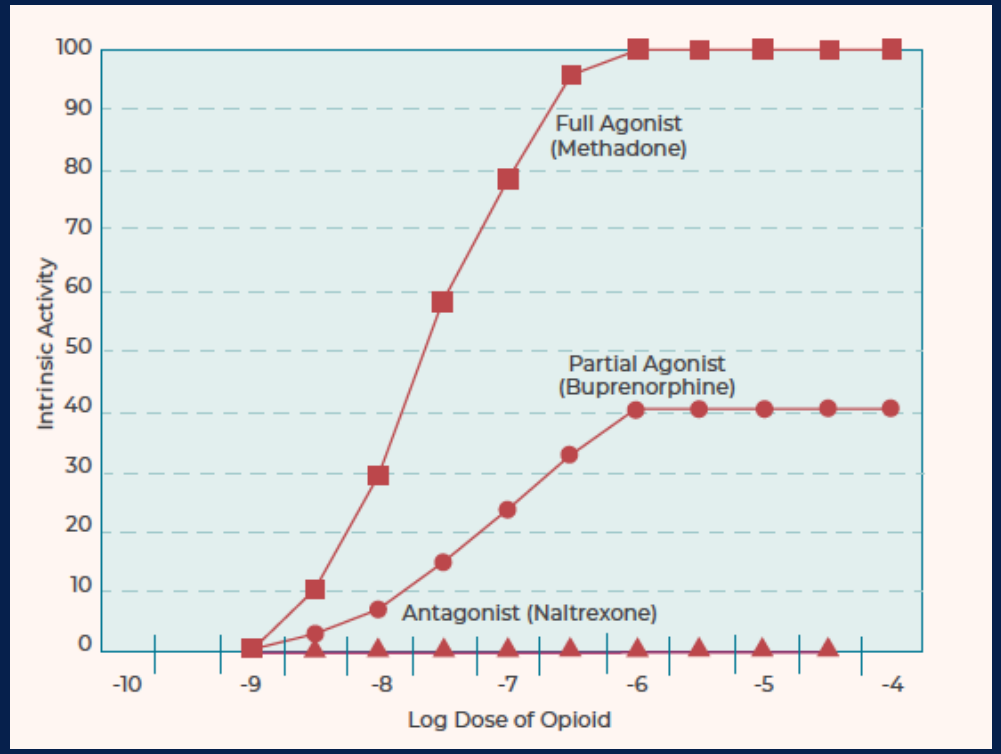
- Transitioning from Methadone to Buprenorphine
- Patients with severe acute pain and OUD
- Non Rx fentanyl use
- Previous unsuccessful attempts at buprenorphine initiation

Mannelli, *Curr Drug Abuse Rev*, 2012
Bissaga, *Addiction,* 2019
Varshneya, J Addict Med, 2021

Silverstein*, Int J Drug Policy*, 2019
Antoine, *Am J Addict*, 2020

Buprenorphine: KEY characteristics

High Affinity

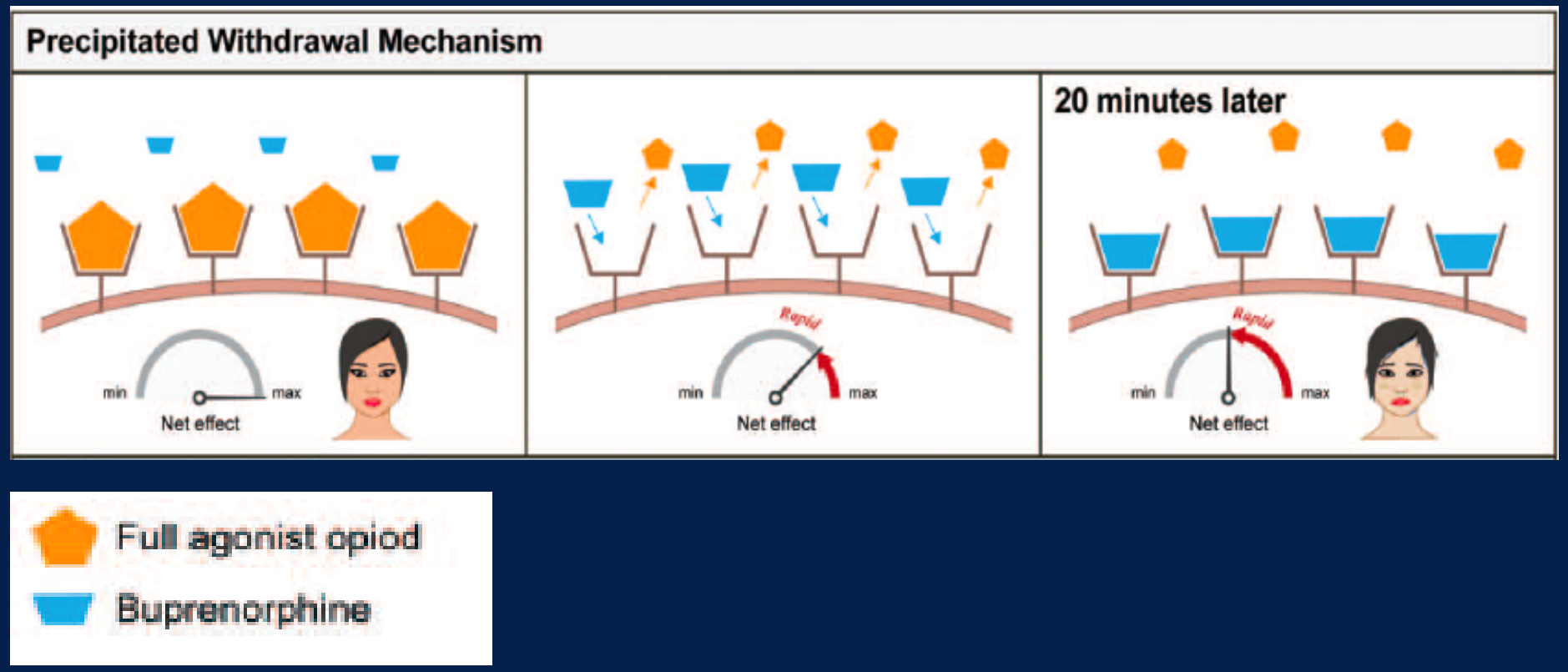


Partial Agonist

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

Precipitated opioid withdrawal

- Partial opioid agonists can cause opioid withdrawal symptoms when introduced to full opioid agonists



Ghosh, *CJA*, 2019

"Classic" Buprenorphine Initiation

Stop full agonists

↓

Wait for withdrawal

COWS > 8-12

↓

Give 1st dose and repeat in 1-2 hours

2-4 mg buprenorphine each dose depending on tolerance

↓

Uptitrate to effective dose over 1-3d

ASAM National Practice Guideline, 2020
SAMHSA, *TIP 63, 2020*

Low dose buprenorphine with opioid continuation (LDB-OC)

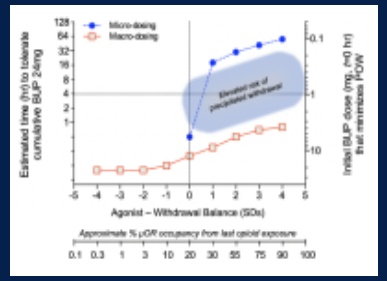
Continue agonist & titrate up buprenorphine with low doses

- Administering small and gradually increasing doses of buprenorphine while *continuing/overlapping* a full agonist opioid over 2-7 days
- Initial doses: typically <2mg buprenorphine
- Many cases & case series (n ~ 250)
- Various buprenorphine formulations used
  - Intravenous
  - Buccal film
  - Transdermal patches
  - SL film or tabs

Cohen, et al. Low Dose Initiation of Buprenorphine: A narrative Review and Practical Approach. Journal of Addiction Medicine, 2021.

Dose predicted to have only small blockade effects with minimal displacement of agonist. The agonism is also minimal. If opioids are not continued, there will be withdrawal

Low dose



Dose that is sufficient to to produce blockade but only generates a weak agonist signal

Middle dose

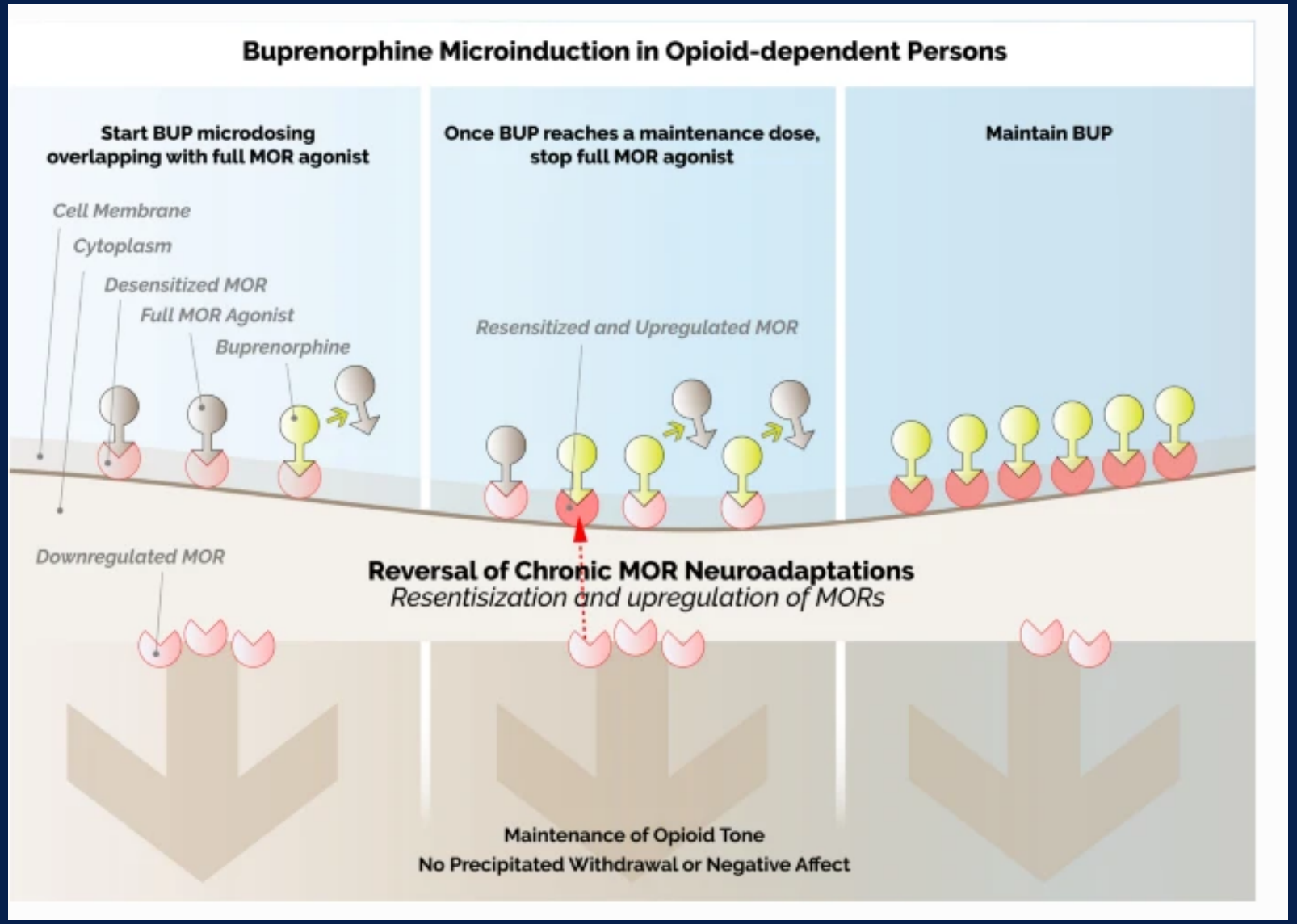
Dose that maximizes the agonist effects of buprenorphine. (no ceiling identified)

High dose

Low Dose Initiation Theory

Buprenorphine causes “re-sensitization” of the opioid receptors

Low dose approach allows Up-regulation of opioid Receptors to prevent opioid withdrawal



De Aquino. *Clin Drug Investig*, 2021

Rationale for Low-Dose Initiation

A **patient-centered** approach that:

- enables clinicians to start buprenorphine without waiting for withdrawal
- allows patients to continue full-opioid agonists for pain
- facilitates faster transitions from methadone
- May reduce the risk of precipitated withdrawal from synthetic opioids with unpredictable clearance

De Aquino et al, *Clin Drug Invest* 2021
Huhn et al, *Drug and Alc Depend 2020*

Principles of low dose buprenorphine initiation

Appropriate clinical situation

Start low

Gradual uptitration

Continue the full agonist

Clear and frequent communication

Pause or slow if withdrawal sx

Care coordination is critical

Cohen, *J Addict Med,* 2021

Example Low Dose Initiation regimen

Day	Buprenorphine/naloxone Dose	Strip/tab Strength	Full Agonist Dose
1	0.5mg ($^1/_4$ strip)	2mg	Continue
2	0.5mg BID ($^1/_4$ strip)	2mg	Continue
3	1mg BID ($^1/_2$ strip)	2mg	Continue
4	2mg BID	2mg	Continue
5	4mg BID	2mg	Continue
6	4mg TID	2mg	Continue
7	8mg BID	8mg	STOP

Case 1 – In hospital acute pain

- 24 year old woman with severe OUD admitted to the hospital with endocarditis now s/p tricuspid valve replacement. Interested in starting buprenorphine.
  - Currently on hydromorphone 8mg PO q3hr as needed for pain hydromorphone 2mg IV q6hrs for breakthrough as well as other adjunctive pain medication
  - Cannot stop opioids in post-op setting for traditional initiation

Questions to consider

- Is her pain controlled?
- Are there non-opioid treatments you can add to her pain regimen?
- Does she have further surgeries?
- What full agonist opioid dose will keep her comfortable during the transition?
- When will she be discharging?

Buprenorphine Dosing Plan - SL

Day	Buprenorphine-naloxone Dose	Tab	Full Opioid Agonist Dose
1	0.5 mg daily	Quarter of 2 mg tab/film	Hydromorphone 8mg Q3H scheduled
2	0.5 mg BID	Half of 2 mg tab/film	Hydromorphone 8mg Q3H scheduled
3	1 mg BID	Full 2 mg tab/film	Hydromorphone 8mg Q3H scheduled
4	2 mg BID	Two 2 mg tabs/film	Hydromorphone 8mg Q3H scheduled
5	4 mg BID*	Half of 8 mg tab/film	Hydromorphone 8mg Q3H scheduled
7	8 mg BID	Full 8 mg film	Stop
8	8mg TID	Full 8mg film	*can restart/continue some opioid if needed

Supportive Medications (ondansetron, loperamide, hydroxyzine, tizanidine, clonidine, dicyclomine)
*Can repeat days if patient develops withdrawal, achiness

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Question

- *Your hospital pharmacy says you can't split films/tab in the hospital?*
- *What other buprenorphine formulations can you use?*

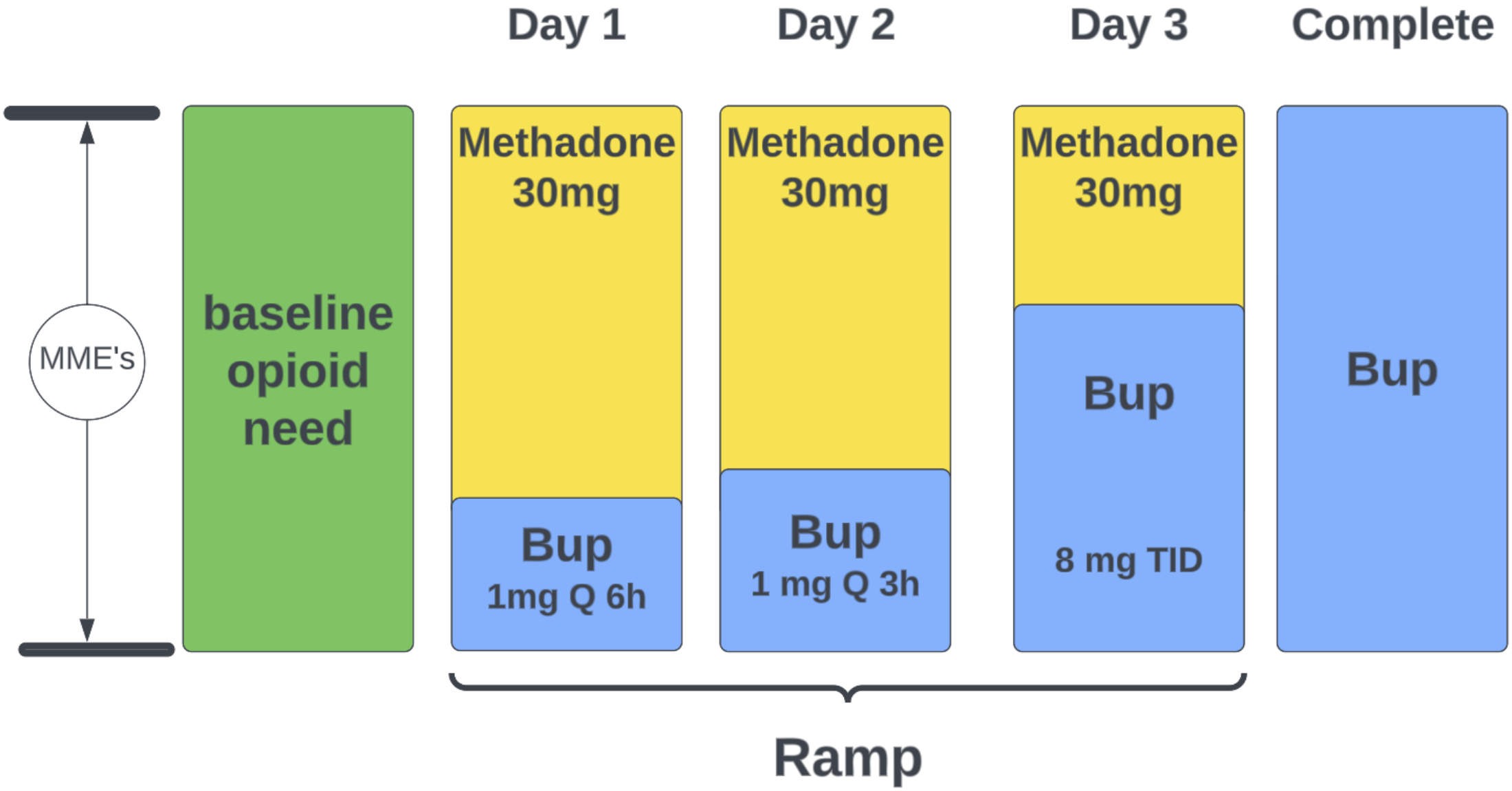
Buprenorphine Dosing Plan – Buccal

Day	Buprenorphine Dose	Buccal Buprenorphine	Full Opioid Agonist Dose
1		225mcg once daily	Same
2		225mcg BID	Same
3		450mcg BID	Same
4	2 mg BID		Same
5	4 mg BID		Same
6	4 mg TID		Same
7	8 mg BID		Off

Question

- Can this be done as an outpatient?

Option – LDB-OC using DEA exemption



Slide courtesy Andrew Herring, MD

Outpatient LDB initiation pearls for practice

Shared decision making with patient, clear information

Ensure ongoing access to full agonist opioid and continue as long as needed

- Do not taper down, or withdrawal will ensue, irrespective of buprenorphine
- This includes any full agonist opioid
- If they do not have ongoing opioid, do not employ LDP

Provide a bubble pack if possible

*Clear and frequent communication with patient

- Provide them with handout for reference, daily call
- Reminder: do not taper down the full agonist
- Help with cutting buprenorphine strips/bubble packs if possible
- Problem solve with them
- Provide comfort meds prn
- Harm reduction
- Cheerlead!

*Pause or slow if withdrawal symptoms, or challenges

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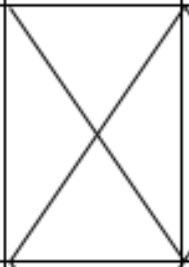
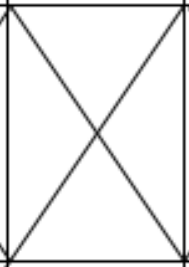
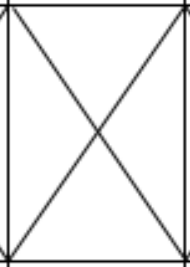
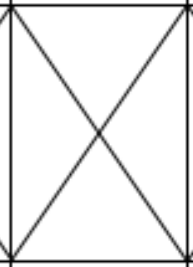
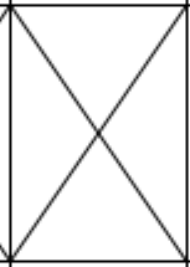
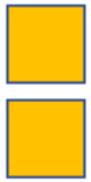
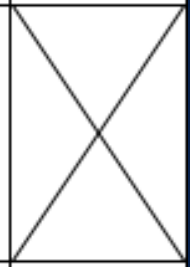
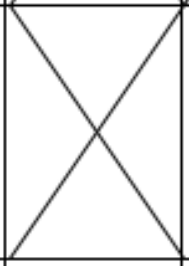
Dosing Guide

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Buprenorphine dose	0.5mg daily	0.5mg BID	1mg BID	2mg BID	4mg BID	4mg TID	8mg BID
Strip size	2mg	2mg	2mg	2mg	2mg	2mg	8mg
Morning dose							
Afternoon Dose							
Night dose							
Full agonist	Continue	Continue	Continue	Continue	Continue	Continue	STOP

1 page guide

Case 2 - methadone

- 45 year old man with severe OUD in sustained remission on methadone 100mg presents to your clinic to discuss transition to buprenorphine
  - Had success with buprenorphine >10 years ago but transitioned to methadone after a period of returning to opioid use
  - Worried about developing cravings and withdrawal if he has to taper methadone
  - Interested in low dose initiation

- Question 1: What would you do with the methadone dose throughout the low dose initiation process?
- Question 2: What would you do if he develops withdrawal symptoms during the transition?
- Question 3: How would you coordinate with the OTP? What might cause the OTP to stop methadone during the low dose transition?

Traditional Methadone-> buprenorphine transition

- High risk for precipitated withdrawal unless down-titrated to 30-50mg
- Down-titration → risk of return to opioid use

SAMHSA TIP 63

Lintzeris, *J Addict Med*, 2018

Buprenorphine Dosing Plan - SL

Day	Buprenorphine-naloxone Dose	Tab	Full Opioid Agonist Dose
1	0.5 mg daily	Quarter of 2 mg tab/film	Methadone 100mg daily
2	0.5 mg BID	Half of 2 mg tab/film	Methadone 100mg daily
3	1 mg BID	Full 2 mg tab/film	Methadone 100mg daily
4	2 mg BID	Two 2 mg tabs/film	Methadone 100mg daily
5	4 mg BID*	Half of 8 mg tab/film	Methadone 100mg daily
7	8 mg BID	Full 8 mg film	Stop
8	8mg TID	Full 8mg film	

Supportive Medications (ondansetron, loperamide, hydroxyzine, tizanidine, clonidine, dicyclomine)
*Can repeat days if patient develops withdrawal, achiness

Final Takeaways/Summary

- Terminology and language is important in our field
- Low dose buprenorphine initiation with opioid continuation is an important new strategy in certain clinical situations
- Low dose buprenorphine initiation with opioid continuation should utilize several guiding principles and may be different in different clinical settings
- Shared decision making with patients is an important component of a successful initiation

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Buprenorphine Dosing Plan - Patch

Day	Buprenorphine Dose	Full Opioid Agonist Dose
1	20 mcg patch	Same
2	1 mg SL BID	Same
3	2 mg SL BID	Same
4	4 mg SL BID	Same
5	6 mg SL BID	Same
6	8 mg SL BID	OFF

Supportive Medications (ondansetron, loperamide, hydroxyzine, tizanidine, clonidine, dicyclomine)

Button D, Hartley J, Robbins J, Levander XA, Smith NJ, Englander H. Low-dose Buprenorphine Initiation in Hospitalized Adults With Opioid Use Disorder: A Retrospective Cohort Analysis. *J Addict Med.* 2021.

Buprenorphine Dosing Plan - IV

Day	Buprenorphine	Full Opioid Agonist Dose
1	0.15 mg IV q6h x2 doses	Same
1	0.3 mg IV q6h x2 doses	
2	0.6 mg IV q6h x2 doses	Same
2	4 mg SL q6h x2 doses	
3	8 mg SL q6h x2 doses	OFF

Supportive Medications (ondansetron, loperamide, hydroxyzine, tizanidine, clonidine, dicyclomine)