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Buprenorphine: low dose inductions and extended release

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Disclosures

Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.

Outline

- ❑ Describe the Fentanyl effect
- ❑ Buprenorphine pharmacology
- ❑ Principles of micro(low dose) induction
- ❑ Current literature
- ❑ Clinical applications

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Clinical scenario: fentanyl use disorder

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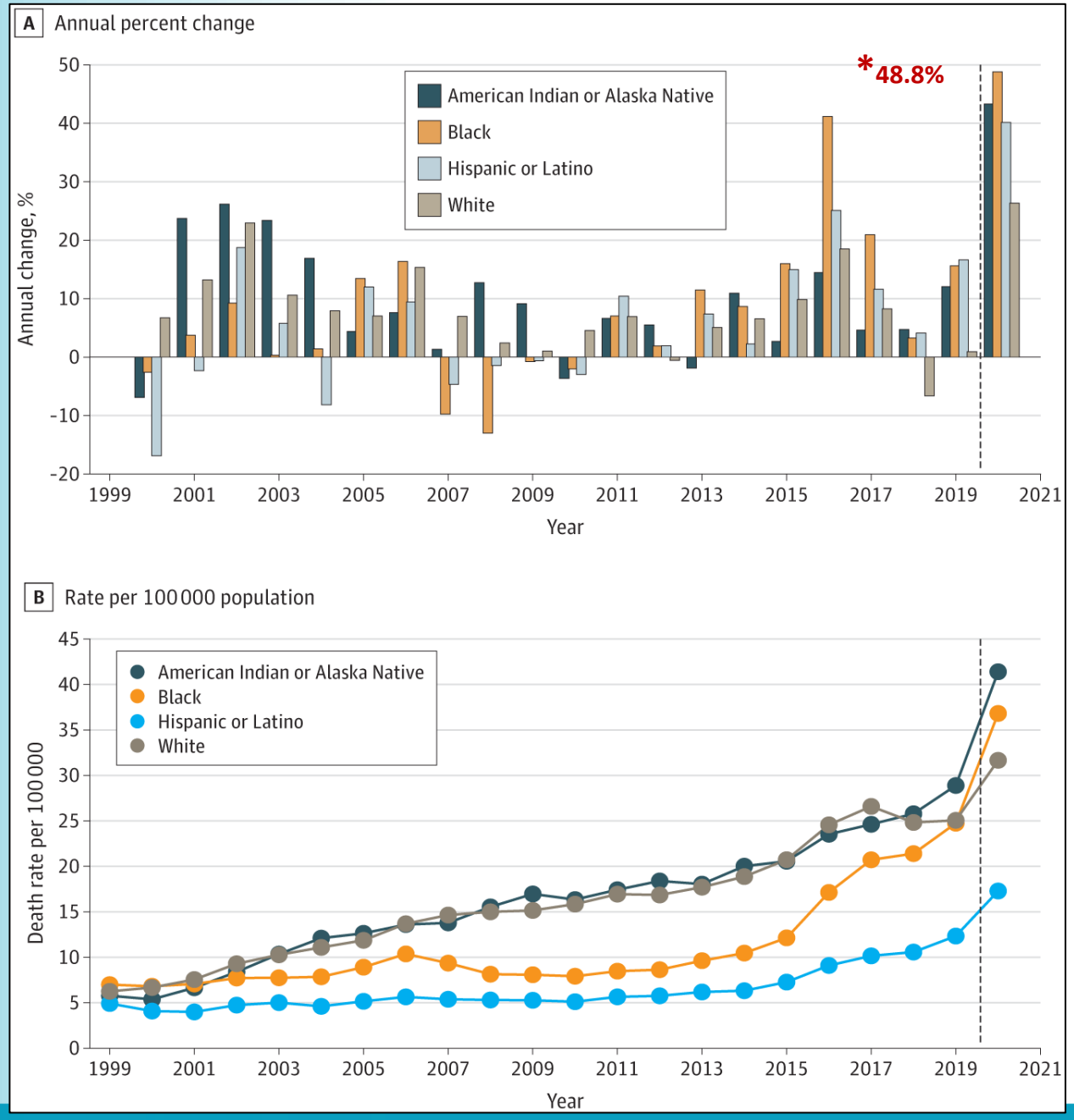
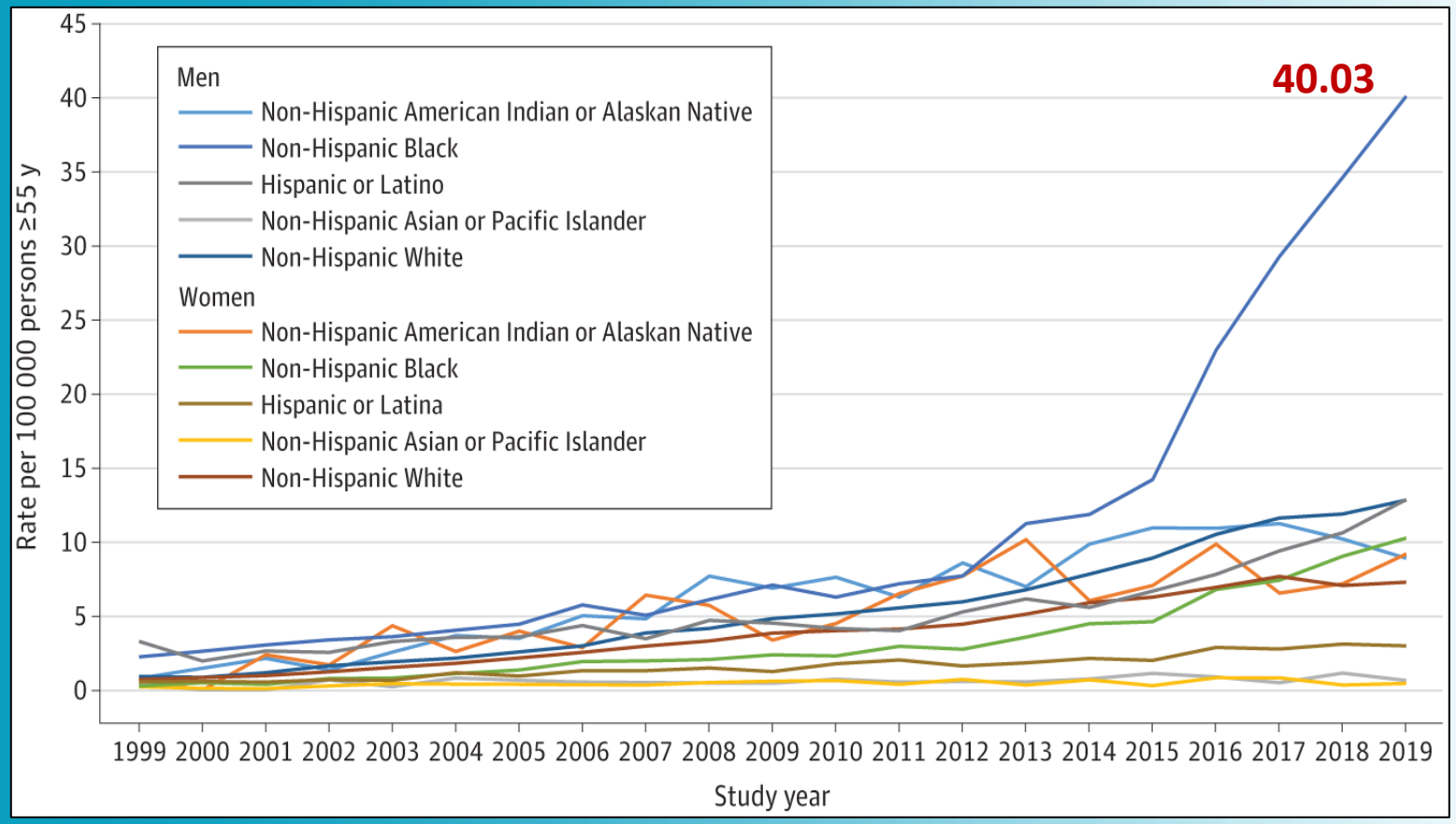
28-year-old Black male complex trauma, reported ADHD, mood disorder, GAD, tobacco use disorder, early onset severe opioid use disorder, severe cocaine use disorder, severe benzodiazepine use disorder c/b withdrawal seizures, h/o involuntary civil commitment twice, active injection fentanyl (2g daily), inhalational cocaine and alprazolam use admitted after Recovery Centers of America called EMS given concerns for intoxication in the context of significant alprazolam use and witnessed brief seizure activity.

The drug overdose mortality gap between white and black individuals reversed for the first time during the pandemic



Evaluation of Increases in Drug Overdose Mortality Rates in the US by Race and Ethnicity Before and During the COVID-19 Pandemic. *JAMA Psychiatry.* Published online March 02, 2022.

Over the past 20 years of the opioid endemic, Black men have suffered disproportionately. In 2019, opioid overdose fatality rate for Black men 4x higher



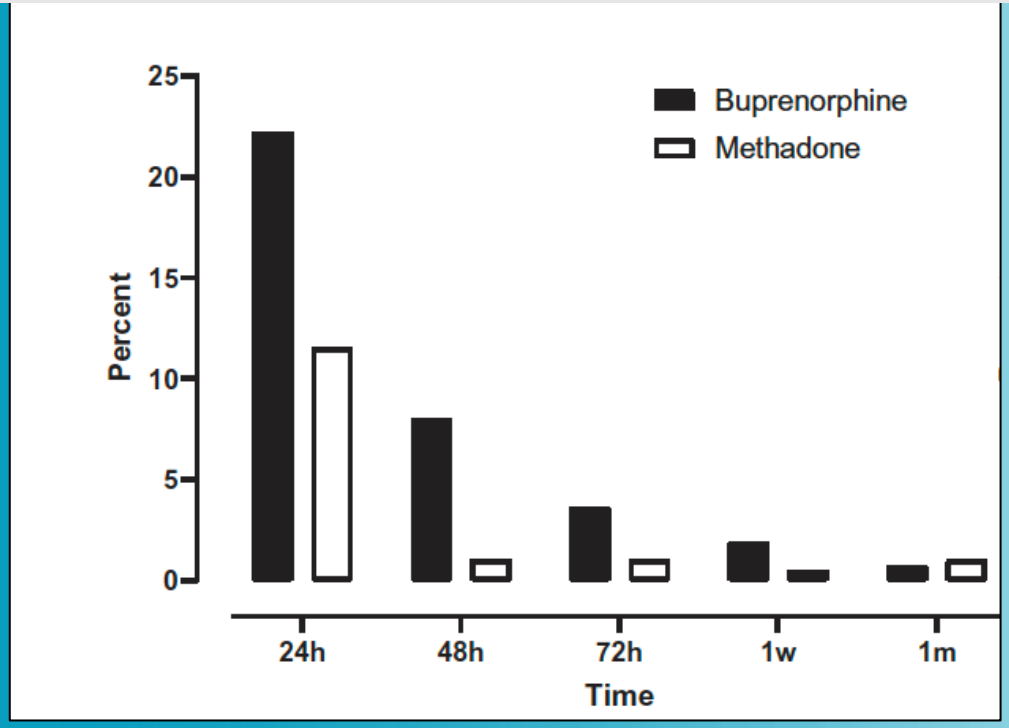
Since 2013, Black men account for the disproportionate increase in rates of opioid overdose deaths for all older adults

CDC identified 3rd wave of epidemic (characterized by the increased presence of fentanyl in the drug supply) marks the onset of increase in opioid overdose fatalities for Black men.

Overall opioid overdose fatality rate 10.7 per 100,000 persons 55+

Mason. Disparities by Sex and Race and Ethnicity in Death Rates due to Opioid Overdose among Adults 55 years or older, 1999-2019. JAMA Network Open. 2022;5(1)

Incidence of buprenorphine-precipitated withdrawal in persons who use fentanyl



37% patients reported severe withdrawal after buprenorphine

- 22% within 24 hours
- 8% within 48 hours

Buprenorphine use (72 hours to 1 week)

- No increase in odds of severe withdrawal

Subset of patients who used buprenorphine and methadone

- 45.4% (buprenorphine) vs 13.2% (methadone) had severe withdrawal

Odds of Severe Opioid Withdrawal Symptoms After Fentanyl Use	Buprenorphine* (N = 685) OR	95% CI	*P*	Methadone† (N = 199) OR	95% CI	*P*
Within 24 h of using fentanyl	5.202	1.979–13.675	0.001	0.616	0.117–3.247	0.568
Within 48 h of using fentanyl	3.352	1.237–9.089	0.017	0.300	0.035–2.606	0.275
Within 72 h of using fentanyl	2.222	0.780–6.329	0.135	0.316	0.036–2.750	0.297
Within 1 wk of using fentanyl	2.133	0.687–6.620	0.190	0.250	0.019–3.342	0.295

Varshneya. Evidence of Buprenorphine-Precipitated Withdrawal in Persons Who Use Fentanyl. *J of Addiction Medicine.* 2021. Publish Ahead of Print.

Short communication

Protracted renal clearance of fentanyl in persons with opioid use disorder

Andrew S. Huhn[a,b,*], J. Gregory Hobelmann[a,b], George A. Oyler[c], Eric C. Strain[a]

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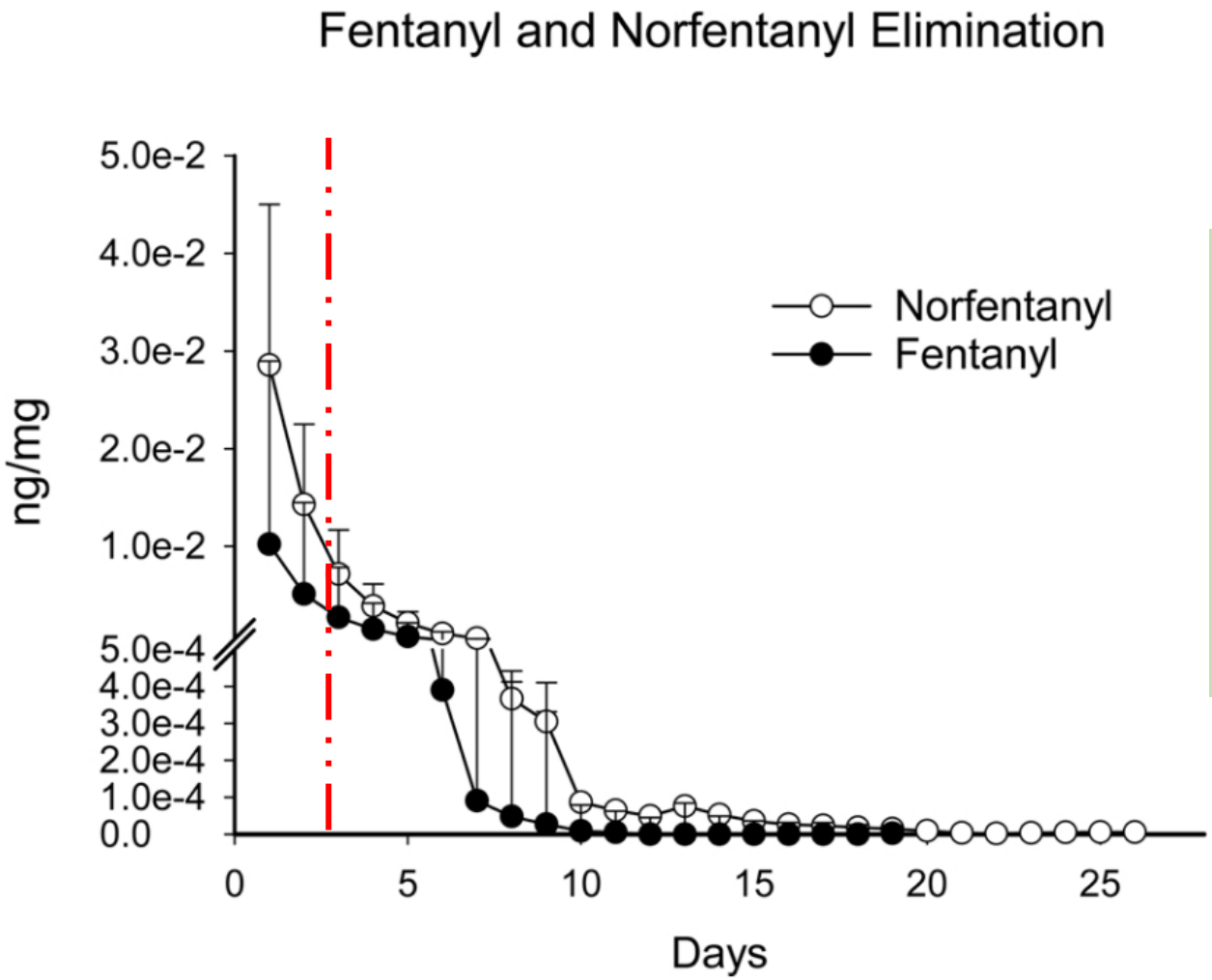
[b] Ashley Addiction Treatment, Havre de Grace, MD, 21078, USA
[c] Department of Chemical and Biomolecular Engineering, Johns Hopkins University, Baltimore, MD, 21218, USA



- Mean Fentanyl clearance **7.7 days**
- Mean Norfentanyl clearance **13.3 days**
- 50% participants, urine norfentanyl >200ng/mL (maximum threshold) **2-3 days after last reported opioid use**

Antoine. Method for Successfully Inducting Individuals Who Use Illicit Fentanyl Onto Buprenorphine/Naloxone. Am J Addict. 2021.

What we have learned about fentanyl

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High potency synthetic opioids (fentanyl and its analogs) have saturated the illicit opioid drug market

Disproportionate etiology of historic drug overdose deaths, especially in racial/ethnic subpopulations, including individuals of color

Fentanyl has a **unique pharmacologic profile**

- highly lipophilic
- rapid CNS and peripheral distribution (high volume of distribution)
- rapid and intense onset of action
- short duration of action (1-2°)

Mechanistically **functions as a long-acting opioid**

- adipose/muscle compartments act as physiologic stores
- rate limiting step for elimination; slow release back to plasma
- prolonged renal clearance with chronic use

Standard buprenorphine induction (initiation) **ineffective**

- high risk of precipitated withdrawal
- high risk of treatment non-engagement
- high risk of post-failure induction morbidity/mortality

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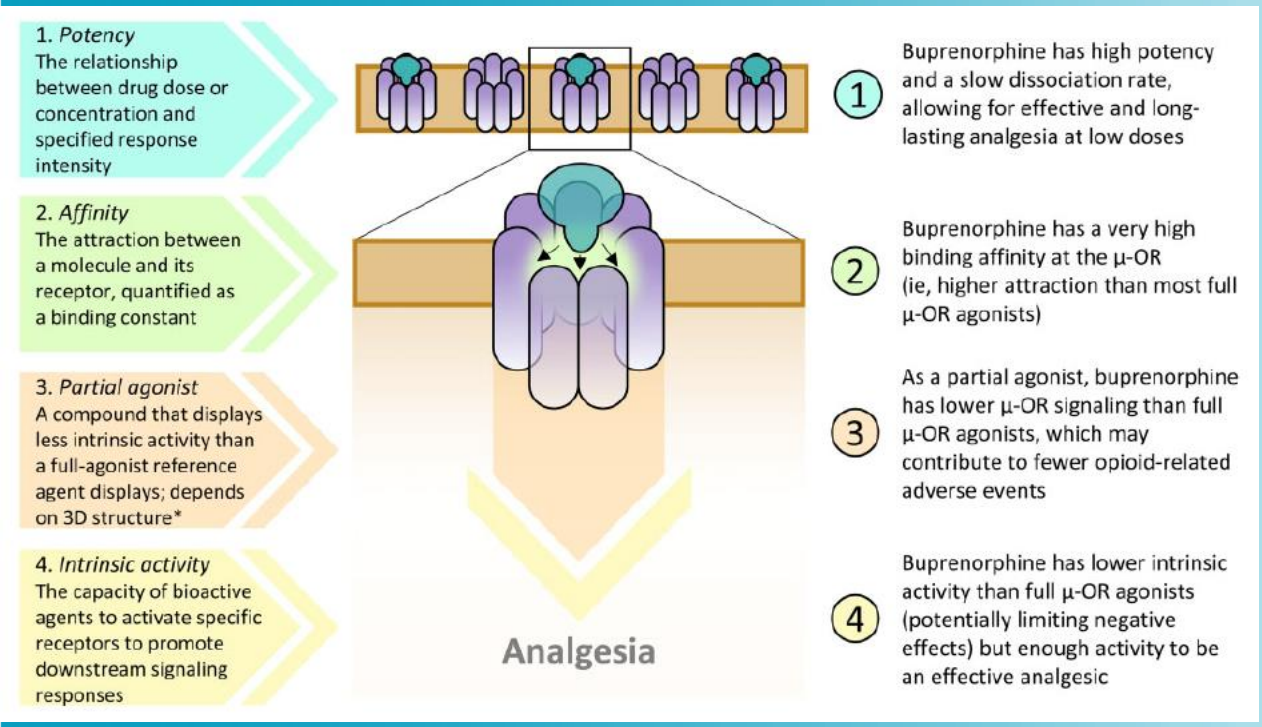
Buprenorphine pharmacology

OR properties



- Mixed agonist-antagonist
  - partial agonist (low intrinsic efficacy/activity)
- Dose-dependent occupancy
- High binding affinity (Ki values <1 nM)
  - 1.7x hydromorphone, 5.4x morphine, 6.2x fentanyl, 120x oxycodone
  - competitive displacement can result in precipitated withdrawal
- Slow **μ**OR dissociation kinetics
  - approximately 166 minutes
  - long half-life (transmucosal half-life w/broad inter-person variability, 24 to 60 hours)
- High potency (20-30x potency of morphine (0.2-0.3mg=10mg morphine)
- **κ**OR (potent agonist, likely antidepressant and antianxiety properties, **δ**OR antagonist, Nociceptin/ORL1 agonist

Buresh. Treating Perioperative and Acute Pain in Patients on Buprenorphine: Narrative Literature Review and Practice Recommendations. *J Gen Int Med*. 2020.
Walton. Clinical Pearls for Buprenorphine Treatment. *Primary Health Care*. 2021.
De Aquino. The Pharmacology of Buprenorphine Microinduction for Opioid Use Disorder. *Clin Drug Investig*. 2021.
Webster. Understanding Buprenorphine for Use in Chronic Pain: Expert Opinion. *Pain Med*. 2020.
Wiegand. Buprenorphine/Naloxone Toxicity. https://emedicine.medscape.com/article/1641147-overview.

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Buprenorphine induction (initiation)

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CADEMY

Standard

- Full opioid agonists are discontinued
- Withdrawal period required, mild-moderate prior to initiation
  - 6-24 hours if short-acting (e.g., heroin)
  - 24-72 hours if long-acting (e.g., methadone)
- Clinical objectives
  - Achieve therapeutic buprenorphine dosing
  - Treat opioid withdrawal symptoms
  - Minimize opioid withdrawal intolerance

Low dose

- Alternative method of buprenorphine initiation
- Full opioid agonists, including non-pharmaceutical opioids, are continued
- Clinical objectives
  - Achieve therapeutic buprenorphine dosing, usually in the context of fentanyl use disorders
  - Minimize opioid withdrawal symptoms
  - Reduce risk of precipitated withdrawal

STAGE	GRADE	PHYSICAL SIGNS/ SYMPTOMS
Early withdrawal Short-acting opioids: 8–24 hours after last use Long-acting opioids: Up to 36 hours after last use	Grade 1	Lacrimation, rhinorrhea, or both Diaphoresis Yawning Restlessness Insomnia
Early withdrawal Short-acting opioids: 8–24 hours after last use Long-acting opioids: Up to 36 hours after last use	Grade 2	Dilated pupils Piloerection Muscle twitching Myalgia Arthralgia Abdominal pain
Fully developed withdrawal Short-acting opioids: 1–3 days after last use Long-acting opioids: 72–96 hours after last use	Grade 3	Tachycardia Hypertension Tachypnea Fever Anorexia or nausea Extreme restlessness
Fully developed withdrawal Short-acting opioids: 1–3 days after last use Long-acting opioids: 72–96 hours after last use	Grade 4	Diarrhea, vomiting, or both Dehydration Hyperglycemia Hypotension Curled-up position

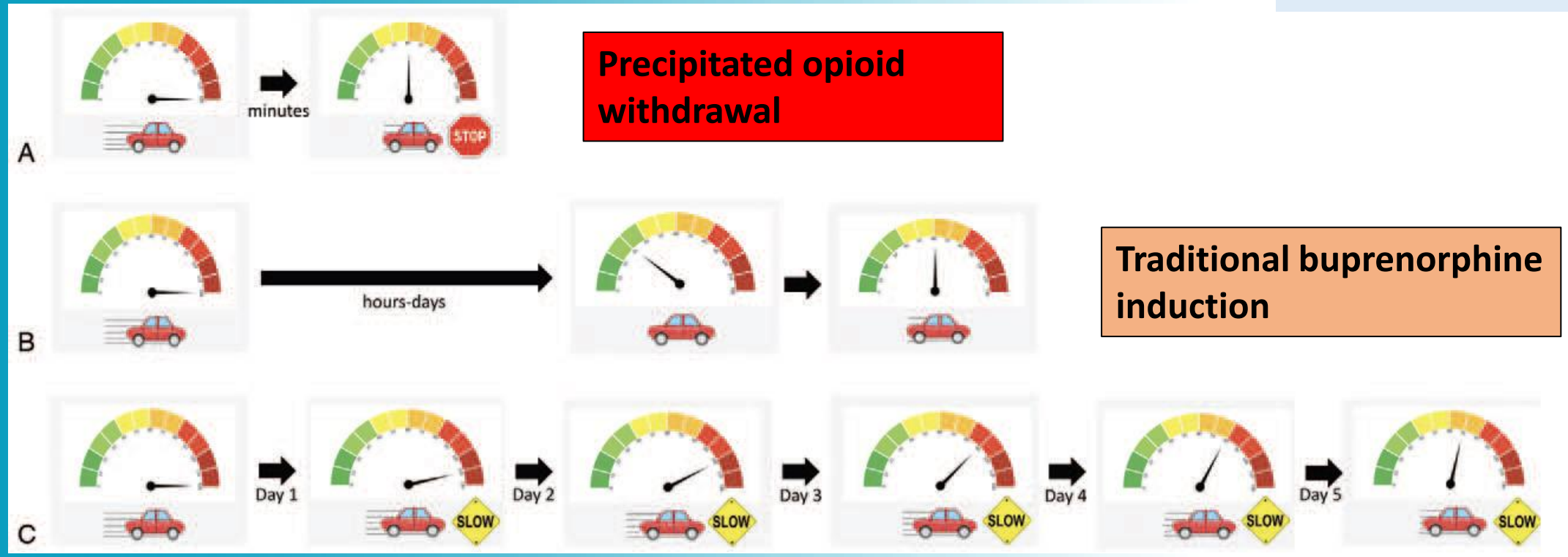
Total duration of withdrawal:

- Short-acting opioids: 7–10 days
- Long-acting opioids: 14 days or more

Car analogy to describe the process of low dose buprenorphine initiation

Car speeding at 120 mph = full opioid agonism

Car at 60 mph = buprenorphine, a partial agonist



Precipitated opioid withdrawal

Traditional buprenorphine induction

Low dose buprenorphine initiation

Cohen et al. Low Dose Initiation of Buprenorphine: A Narrative Review and Practical Approach. *J of Addiction Medicine*, vol. Publish Ahead of Print, 2021

Buprenorphine micro(low dose) induction concept (cross-over method)

Step 1: **Overlapping**/Concurrent full agonist opioid(s)

Step 2: **Bridge** (incremental small doses of buprenorphine, gradual change in net μ-receptor activation)

Step 3: **Cross-titration** (full agonist opioids discontinued/tapered; normal dose buprenorphine)

Mortaji. Advanced Inpatient Management of Opioid Use Disorder in a Patient Requiring Serial Surgeries. *J Gen Int Med*. 2021.
Ghosh. A review of novel methods to support the transition from methadone and other full agonist opioids to buprenorphine/naloxone sublingual in both community and acute care settings. *Can J Addict*. 2019.
Hämmig. Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method. *Subst Abuse Rehabil*. 2016.
Terasaki et al. Transitioning hospitalized patients with opioid use disorder from methadone to buprenorphine without a period of opioid abstinence using a microdosing protocol. Pharmacotherapy. 2019.
Martin et al. Case Report: "Striving to Skip the Withdrawal" Using Buprenorphine–Naloxone Microdosing for Hospitalized Patients. Canadian J Addiction. 2019.

Spectrum of difficulty and risk for adverse consequences

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Clinical scenarios and low dose buprenorphine initiations

Cohen et al. Low Dose Initiation of Buprenorphine: A Narrative Review and Practical Approach. J Addict Med. 2021.

Buprenorphine Induction Strategies (dosing based)

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Standard
Initial dosing: 2-4mg
Day 1 total: 6-12mg

Low dose
Initial dosing: 0.5-1mg
Day 1 total: 0.5-2mg

Micro-dose
Initial dosing: 0.02-0.25mg
Day 1 total: 0.25-0.48mg

Macro-dose
Initial dosing: 4-8mg
Day 1 total: 16-32mg

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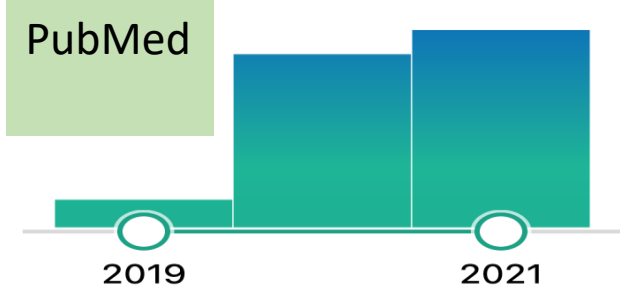
Systematic review

General overview (3 studies, 142 patients)

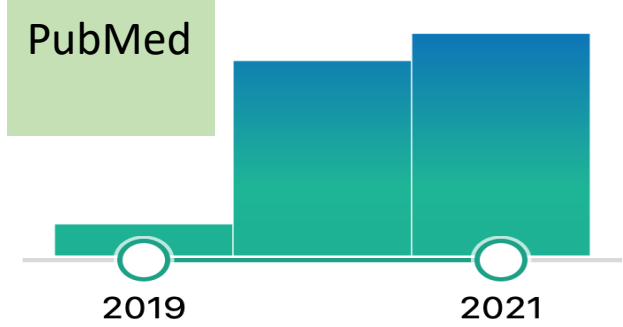


- Limited evidence (small sample sizes, case series/reports, variable selection criteria, poor quality/methodology, significant heterogeneity, multiple dosing regimens, U.S and Canada)[2,3]
- Buprenorphine initiated for OUD alone or in combination with pain in the outpatient and inpatient settings[1,2,3]
- Transitions to buprenorphine include chronic opioid use for pain, methadone for opioid use disorders and illicit opioid withdrawal and illicit opioid use (alone and with methadone)[3]
- No comparative efficacy or safety studies[2,3]

[1] Ahmed. Microinduction of Buprenorphine/Naloxone: A Review of the Literature. *Am J Addict*. 2021.
[2] Moe. Effectiveness of micro-induction approaches to buprenorphine initiation: A systematic review protocol. *Addictive Behaviors.* 2020.
[3] Adams. Initiating buprenorphine to treat opioid use disorder without prerequisite withdrawal: a systematic review. *Addict Sci Clin Pract*. 2021.

Systematic review

Protocol specifics

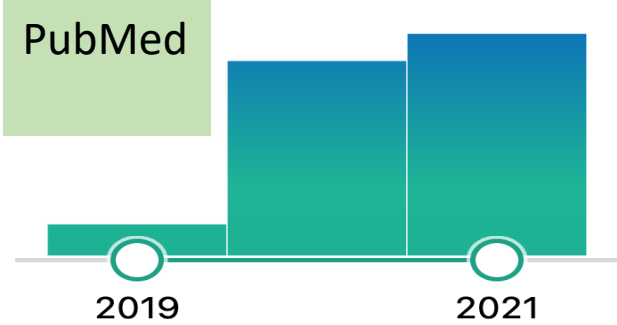


- Range of initiation strategies
  - micro-dosing >> buprenorphine transdermal bridge (1 case fentanyl patch bridge, 2 sustained release oral morphine)[3]
  - Initial doses 0.03-1mg (median 0.5mg), maintenance dose 8-32mg (median 16mg)1,[2,3]
  - **daily mean rate dose Δ to reach TDD 8mg = 1.36mg/d**
  - wide variation regimen durations, median 6d (3-112d)[2,3]
  - 88% reached therapeutic buprenorphine dose, median 8 days[3]
- Overlapping opioid agonists[3]
  - 26% methadone, 22% hydromorphone, 22% fentanyl, 17% multiple, 13% morphine[2]
  - Median MME daily doses[2]
    - Day 1 300mg (106-1025mg), day 2 280mg (96-900), day 3 320mg (144-1050mg)

[1]Ahmed. Microinduction of Buprenorphine/Naloxone: A Review of the Literature. *Am J Addict*. 2021. [2]Moe. Effectiveness of micro-induction approaches to buprenorphine initiation: A systematic review protocol. *Addictive Behaviors.* 2020. [3]Adams. Initiating buprenorphine to treat opioid use disorder without prerequisite withdrawal: a systematic review. *Addict Sci Clin Pract*. 2021.

Systematic review

Withdrawal incidence



- Few studies standardized methods[2]
- 95% of studies reported no precipitated W/D[2]
- 58% patients reported W/D (8% moderate)[3]
- Difficult to separate W/D secondary to buprenorphine under-dosing versus precipitated W/D
- **Subgroup analysis (8 studies, 11 patients, methadone overlap)**
  - **5% (3 patients) reported precipitated W/D[2]**

[1]Ahmed. Microinduction of Buprenorphine/Naloxone: A Review of the Literature. *Am J Addict*. 2021. [2]Moe. Effectiveness of micro-induction approaches to buprenorphine initiation: A systematic review protocol. *Addictive Behaviors.* 2020. [3]Adams. Initiating buprenorphine to treat opioid use disorder without prerequisite withdrawal: a systematic review. *Addict Sci Clin Pract*. 2021.

Buprenorphine low dose research

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Emerging research

- case reports, case series
- significant heterogeneity
  - patient scenarios
  - dosing protocols

Wong, James S H et al. "Comparing rapid micro-induction and standard induction of buprenorphine/naloxone for treatment of opioid use disorder: protocol for an open-label, parallel-group, superiority, randomized controlled trial." *Addiction science & clinical practice* vol. 16,1 11. 12 Feb. 2021, doi:10.1186/s13722-021-00220-2

First randomized controlled trial comparing the effectiveness and safety of rapid micro-induction versus standard induction of buprenorphine/naloxone. Open label superiority trial, eligible patients with OUD will be randomized to either: (a) the rapid micro-induction arm or (b) the standard induction arm (treatment as usual). British Columbia and Vancouver General Hospital. The Complex Pain and Addiction Services (CPAS) is a consulting service in which VGH inpatients with substance use disorders are referred to for treatment and counselling. The primary objective is to compare rapid micro-induction versus standard induction on the successful induction of buprenorphine/naloxone with low levels of withdrawal in patients with OUD. The secondary objectives are to evaluate treatment retention, illicit drug use, self-reported drug use behavior, craving, pain, physical health, safety, and client satisfaction. The rapid micro-induction arm will involve the administration of buprenorphine/naloxone and hydromorphone, while the standard induction arm will involve the administration of only buprenorphine/naloxone. N=50.

Low Dose Buprenorphine Induction with Full Agonist Overlap in Hospitalized Patients with Opioid Use Disorder: A Retrospective Cohort Study. Journal of Addiction Medicine. Dec 2021.

- Primary outcome: therapeutic BUP at discharge and a plan for outpatient BUP f/u
  - Overall,
    - 83% (N=51) successful transition to BUP
- Secondary outcomes
  - Duration low dose protocol mean 8d (2-35d)
  - 39% (N=22) identified w/d symptoms (minor, included anxiety, diaphoresis, headaches)
    1) reported withdrawal symptoms
    2) 30-d f/u to an outpt BUP program
  - 48% (N=30) discharged with full opioid agonists
  - 37% (N=23) discharged on BUD and full agonists
- Low dose with full agonist overlap duration
  - 66% (21/35 same healthcare system referrals) followed up within 30d of hospital discharge
- Median LOS 28d w/ successful transition (43d w/o, NS)

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. Low Dose Buprenorphine Induction With Full Agonist Overlap in Hospitalized Patients With Opioid Use Disorder: A Retrospective Cohort Study. J Addict Med. 2021 Dec 23.

TABLE 2. Patient Characteristics and Outcomes

Variable	Successful (n = 51)	Unsuccessful (n = 11)	Total (N = 62)	*P*
Age in years, mean (range)	42 (21–69)	53 (38–67)	44 (21–69)	<0.01
Sex				0.08
M	33 (65%)	4 (36%)	37 (60%)	
F	18 (35%)	7 (64%)	25 (40%)	
Ethnicity				0.45
Hispanic	2 (4%)	1 (9%)	3 (5%)	
Not Hispanic	49 (96%)	10 (91%)	59 (95%)	
Race/Ethnicity*				0.23
White	46 (90%)	8 (73%)	54 (87%)	
Black/African American	3 (6%)	2 (18%)	5 (8%)	
Hispanic	2 (4%)	1 (9%)	3 (5%)	
Asian				
American Indian/Alaska Native				
Other				
Length of stay in days, median (S				
Concurrent non-opioid substance				
Reason for transition				
Post-hospital placement				
Patient preference/Request				
Patient requests to switch from				
Safety concerns*				
Full Agonist at time of switch†				
Methadone started during hospi				
Methadone for OUD treatment				
Oxycodone				
Hydromorphone				
Fentanyl				
Other				
Full agonist MED, median (SD),				
Any withdrawal symptoms reporte				

*Safety concerns included: long Q
†Not mutually exclusive.

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Lessons

- Patient motivation, preference and confidence in process are important predictors of success (95% of patients able to transition to therapeutic BUP with low dose BUP+full opioid agonist overlap)
- **43% of patients (facilitate posthospital placement) unsuccessful**
- **5% of patients (patient preference/request) unsuccessful**
- **14% (methadone MOUD to BUP) unsuccessful**
- **Low dose buprenorphine is an effective treatment engagement tool**

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Methods of low dose buprenorphine initiations, formulations

Rapid method

Splitting method, method of choice

Intravenous method

Patch method

Buccal method

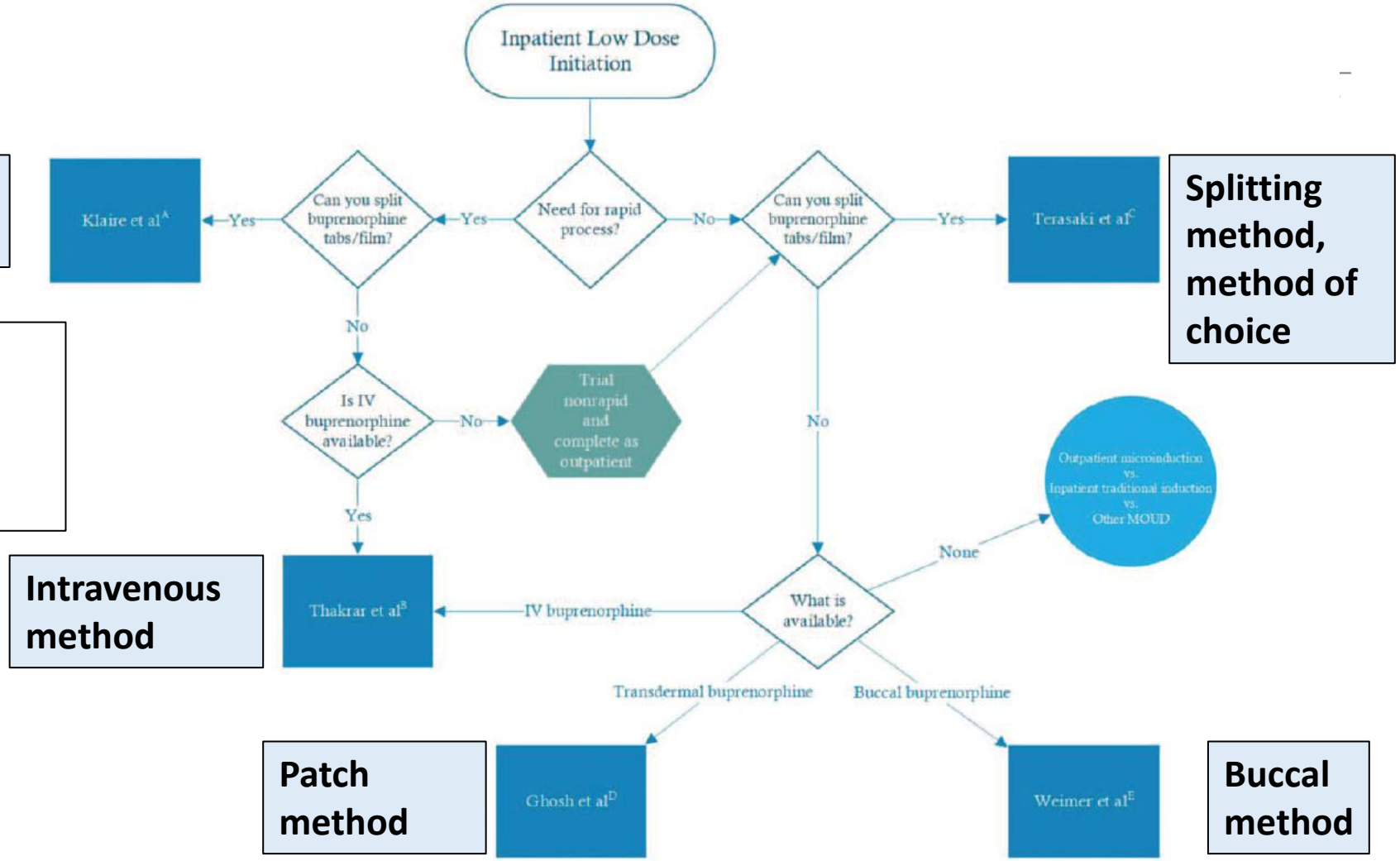


FIGURE 3. Flowchart of hospital-based low dose initiation protocols. **A**, Rapid method (Klaire et al[30,45]): Day 1 - 0.5 mg SL q3h, Day 2 – 1 mg SL q3h, Day 3 - 8–16 mg SL and additional PRN. **B**, Intravenous method (Thakrar et al[34]): Day 1 - 0.15 mg IV q6h, Day 2 - 0.3 mg q6h, Day 3 - 0.6 mg IV q6h, Day 4 - 4 mg SL q6h, Day 5 - discharge dose. **C**, Splitting method (Terasaki et al[33]): Day 1 - 0.5 mg SL daily, Day 2 - 0.5 mg SL q12h, Day 3 - 1 mg SL q12h, Day 4 - 2 mg SL q12h, Day 5 - 4 mg SL q12h, Day 6 - 8 mg SL qd, Day 7 - 8 mg SL QAM and 4 mg SL QPM, Day 8 - 12 mg SL daily. **D**, Patch method (Ghosh et al[43]): Variable doses and strategies. **E**, Buccal method (Weimer et al[26]): Day 1 - 225 mcg buccal daily, Day 2 - 225 mcg buccal q12h, Day 3 - 450 mcg buccal q12h, Day 4 - 2 mg SL q12, Day 5 - 4 mg SL q12, Day 6 - 4 mg SL q8, Day 7 - 8 mg SL q12h. IV indicates intravenous; SL, sublingual.

Cohen et al. Low Dose Initiation of Buprenorphine: A Narrative Review and Practical Approach. J Addict Med. 2021 Dec 23. Epub ahead of print.

Hospital clinical scenarios appropriate for low-do buprenorphine initiati

Table 3. Practice Considerations for Hospital-based Low-dose Buprenorphine Initiation

Clinical Scenario (With References)	Low-dose Buprenorphine Initiation Practice Considerations
Acute, severe illness[18,34]	Severe, acute illness makes opioid withdrawal challenging to tolerate. The low-dose buprenorphine initiation schema offers an opportunity to start buprenorphine during this period. 1. Perform standard low-dose buprenorphine initiation protocol with close communication between the medical care team and the patient. This protocol can be extended to reduce withdrawal symptoms if they occur. 2. Pay special attention to the patient taking sedatives or the patient with respiratory depression. However, low-dose buprenorphine initiation allows for greater titration and symptom control, so we do not recommend foregoing low-dose initiation for these patients.
Co-occurring pain[10,14,17,18,21,22]	For the patient with co-occurring pain, we recommend maximizing pain control during the low-dose initiation period. These principles apply to the patient in the perioperative period, including those undergoing emergency surgeries. Buprenorphine is well tolerated in the perioperative setting. 1. Provide as-needed doses of high affinity, full-agonist opioids (e.g., hydromorphone) either intravenously or orally for breakthrough pain. 2. Extend the low-dose initiation protocol duration if patients experience greater than expected pain. 3. Dosing buprenorphine three times per day affords improved analgesia.
History of precipitated withdrawal[7,17,19,37]	If patients have a history of precipitated withdrawal, this can provoke an intense post-traumatic stress response that may mimic withdrawal and include symptoms such as palpitations, anxiety, sweating, nausea. Low-dose initiation can provide an alternative path to buprenorphine initiation, though it may require additional considerations, including: 1. Take extra time to educate patients about the physiology of precipitated withdrawal and explain how low-dose initiation addresses these past issues. 2. Partner closely with nurses and the patient to implement strategies to reduce anxiety, including maximizing adjunctive medications.
Opioid withdrawal intolerance[5,10,14]	ASAM guidelines recommend a COWS score of 11–12 or more (mild to moderate withdrawal) to indicate sufficient withdrawal to allow a safe and comfortable traditional buprenorphine initiation. For many patients, mild acute withdrawal with COWS less than 10 is uncomfortable enough for them to want to leave the hospital against medical advice. 1. Offer adjunctive medications and low dose methadone for acute withdrawal while simultaneously offering low-dose buprenorphine initiation. We routinely start 40 mg methadone, place a buprenorphine patch, and proceed with standard low-dose initiation. 2. Once patients reach therapeutic buprenorphine doses, patients can stop methadone.
Transition from methadone to buprenorphine[9,10,21]	For patients taking high dose methadone, we recommend an extended low-dose buprenorphine initiation due to the long half-life of methadone (Table 4). 1. We have found that patients do well with 80 mg of methadone before starting low-dose buprenorphine initiation. Consider tapering to 80 mg of methadone before low-dose initiation if they are taking higher doses. 2. Prepare patients for the possibility that they may feel mild withdrawal during low-dose initiation and for some time after transition and offer adjunctive medications. 3. Taper methadone in collaboration with the patient. We regularly begin the taper on day three and discontinue methadone by day 10.
Rapid hospital discharge[14,20]	There is little evidence to inform the optimal duration of low-dose initiation. Experience supports that a slower schedule may be easier to tolerate. However, hospital discharge can be unpredictable. For patients who are scheduled to discharge quickly, there are several options. 1. Rapid low-dose initiation over three days, beginning with immediate buprenorphine patch placement. 2. Provide prescription for full low-dose buprenorphine initiation to complete at home. a. Provide detailed patient instructions with teach-back. b. Communicate with outpatient providers to ensure their understanding of and rationale for low-dose buprenorphine initiation.

Button et al. Low-dose Buprenorphine Initiation in Hospitalized Adults with Opioid Use Disorder: A Retrospective Cohort Analysis. *J Addiction Med*. 2022.

Clinical scenario: Rapid low dose buprenorphine initiation

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

28-year-old Black male complex trauma, reported ADHD, mood disorder, GAD, tobacco use disorder, early onset severe opioid use disorder, severe cocaine use disorder, severe benzodiazepine use disorder c/b withdrawal seizures, h/o involuntary civil commitment twice, active injection fentanyl (2g daily), inhalational cocaine and alprazolam use admitted after Recovery Centers of America called EMS given concerns for intoxication in the context of significant alprazolam use and witnessed brief seizure activity.

He received methadone for three days, initial total dose of **60mg followed by 40mg daily for two days with effective management of his opioid withdrawal symptoms**.

Multiple attempts at buprenorphine self-induction. He agreed to rapid buprenorphine induction with plan for depot buprenorphine prior to discharge given plans for CSS placement.

He received **SL buprenorphine 0.5mg Q3 for 8 doses (2mg over 2 days), 1mg Q3 for 8 doses (4mg over 3 days) then 8mg daily**. No withdrawal symptoms.

He was discharged to a CSS program on buprenorphine-naloxone 8mg TID (could not receive Sublocade because of his insurance).

UCSF outpatient rapid low dose buprenorphine initiation (3-day ROI) protocol

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

TABLE 1. Overview of Available Buprenorphine Initiation Protocols at San Francisco Office-based Buprenorphine Induction Clinic

Initiation Day	Buprenorphine Initiation Protocols		
	Traditional Buprenorphine Initiation	6–7 Day Standard Low Dose Overlap Initiation Protocol	3-day Rapid Overlap Initiation Protocol
Day 0	Begin abstaining from all full agonist opioids	Continue full agonist opioid use	Continue full agonist opioid use
Day 1	Start BUP-NX 4–8 mg if adequate withdrawal symptoms. Provide additional 4–8 mg dose 6–8 hours later if still in withdrawal	0.5 mg SL BUP once	0.5 mg SL BUP every 6 hours (total dose 2 mg)
Day 2	Take total dosage from day 1 in the morning. Follow up with the provider.	0.5 mg SL BUP BID	1 mg SL BUP every 6 hours (total dose 4 mg)
Day 3		0.5 mg SL BUP in the morning, 1 mg SL BUP-NX in afternoon and evening	2 mg SL BUP every 6 hours (total dose 8mg)
Day 4		2 mg SL BUP-NX BID	12 mg SL BUP-NX in the morning and follow up with the provider.
Day 5		4 mg SL BUP-NX BID	
Day 6		12 mg SL BUP-NX in the morning and follow up with the provider.	
Risk of precipitated withdrawal	High	Low	Low

BUP indicates buprenorphine monoproduct; BID, two times a day; BUP-NX, buprenorphine-naloxone; SL, sublingual.

11/12 individuals with severe fentanyl use disorders

- **92% previous mOUD**
- **75% inhalational use, 25% injection and insufflation use**
- **Opted for ROI**
  - **fentanyl use>>hx/fear of precipitated w/d**
- **All individuals continued to use non-prescribed full opioid agonists**

Suen et al. Rapid Overlap Initiation Protocol Using Low Dose Buprenorphine for Opioid Use Disorder Treatment in an Outpatient Setting. Journal of Addiction Medicine. Publish Ahead of Print.

UCSF outpatient rapid low dose bupreno initiation (3-day ROI) protocol

- All patients completed ROI retained in care
- 45% retained in treatment
- 33% achieved 2-weeks of abstinence
- Prioritize patient-centered decision making
- Manage expectations
- Overdose prevention strategies/harm reduction practices important
- Co-location w/ CBHS Pharmacy key
  - standardized blister packaging (simplicity)
- 25% transitioned to ER buprenorphine

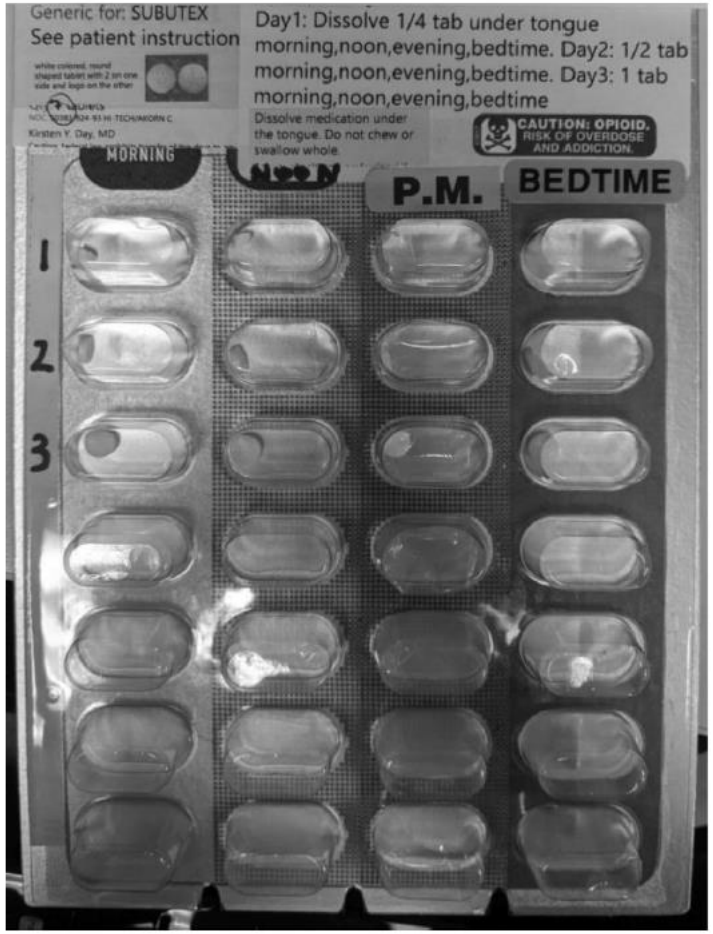


FIGURE 1. Blister packaging of buprenorphine doses using 3-day rapid overlap initiation protocol. The blister packaging offers 4 columns to include dosing in the morning, noon, afternoon, and at bedtime. Each row denotes a separate day for the initiation process. Row 1 (Day 1) has 1/4 tab of the 2 mg buprenorphine sublingual mono-formulated product in each bubble. Row 2 (Day 2) has 1/2 tab in each bubble. Row 3 (Day 3) has 1 tab in each bubble.

Suen et
Disorde
Print.

Clinical scenario: readmission and reconnection

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

28-year-old Black male complex trauma, reported ADHD, mood disorder, GAD, tobacco use disorder, early onset severe opioid use disorder, severe cocaine use disorder, severe benzodiazepine use disorder c/b withdrawal seizures, h/o involuntary civil commitment twice, active injection fentanyl (2g daily), inhalational cocaine and alprazolam use admitted after Recovery Centers of America called EMS given concerns for intoxication in the context of significant alprazolam use and witnessed brief seizure activity.

He returned to use 2 weeks later (fentanyl and benzodiazepines), **contacted me and returned to our ED**. He received methadone 40mg daily for three days, underwent rapid buprenorphine micro-induction.

Primary care connected to MGH. Immediate post-discharge initial visit MGH Bridge clinic visit, **received first dose of Sublocade 300mg**. Second dose one month later.

Bridge clinic follow-up 3 months later (actively injecting), received test dose of SL buprenorphine then Sublocade 300mg. He received a subsequent dose one month later.

Extended release buprenorphine

Sublocade®

Monthly formulation (100mg, 300mg)

– Phase 3 trial: mean abstinence 41.3%, 42.7% (300/100mg), placebo 5% (p>0.001 for both doses)

– subset of patients need SL buprenorphine-naloxone supplementation up to 4 months

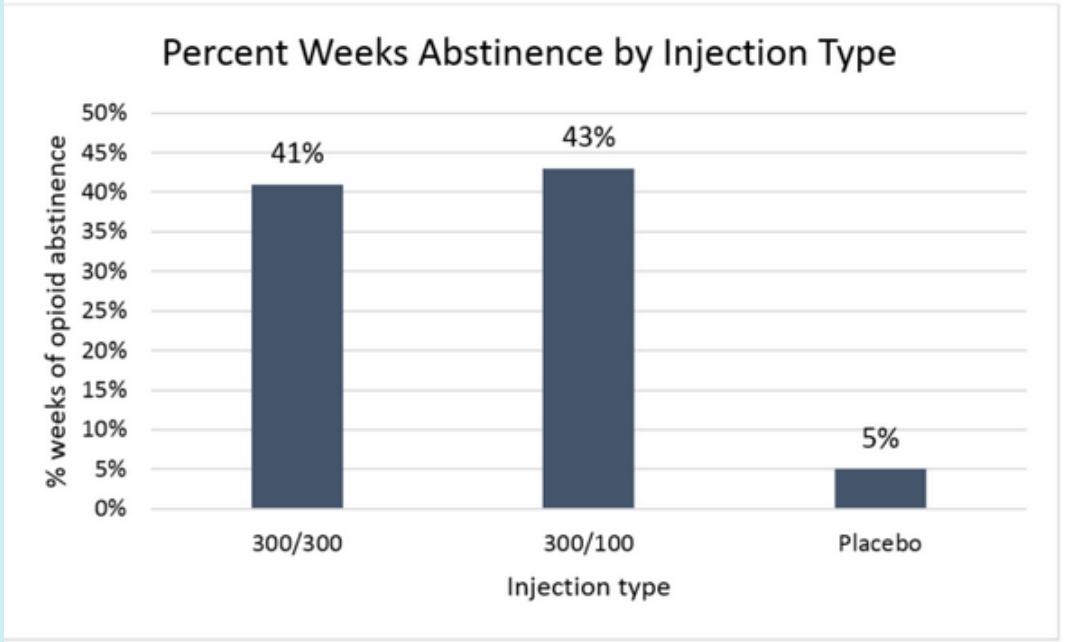
Brixadi®

– FDA NDA resubmission for Dec 2022

– Phase 3 trial: superior to SL buprenorphine-naloxone (greater percentage of negative opioid assessment weeks 4 to 24, (26.7% vs 6.7%; P = 0.008)

Buvidal®

– approved in Europe; weekly (8mg, 16mg, 24mg, 32mg) and monthly formulations (64mg, 96mg, 128mg)



Lofwall. Weekly and monthly subcutaneous buprenorphine depot formulations vs daily sublingual buprenorphine with naloxone for treatment of opioid use disorder: a randomized clinical trial. JAMA Intern Med. 2018;178:764–773

Peckham . Real-world outcomes with extended-release buprenorphine (XR-BUP) in a low threshold bridge clinic: a retrospective case series. J Subst Abuse Treat. 2021;126:108316. doi:10.1016/j.jsat.2021.108316

Moreno. Sublingual buprenorphine plus buprenorphine XR for opioid use disorder. *Current Psychiatry*. 2022 June;21(6):39-42.

Haight. RB-US-13-0001 Study Investigators. Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2019;10174(393):778-790.

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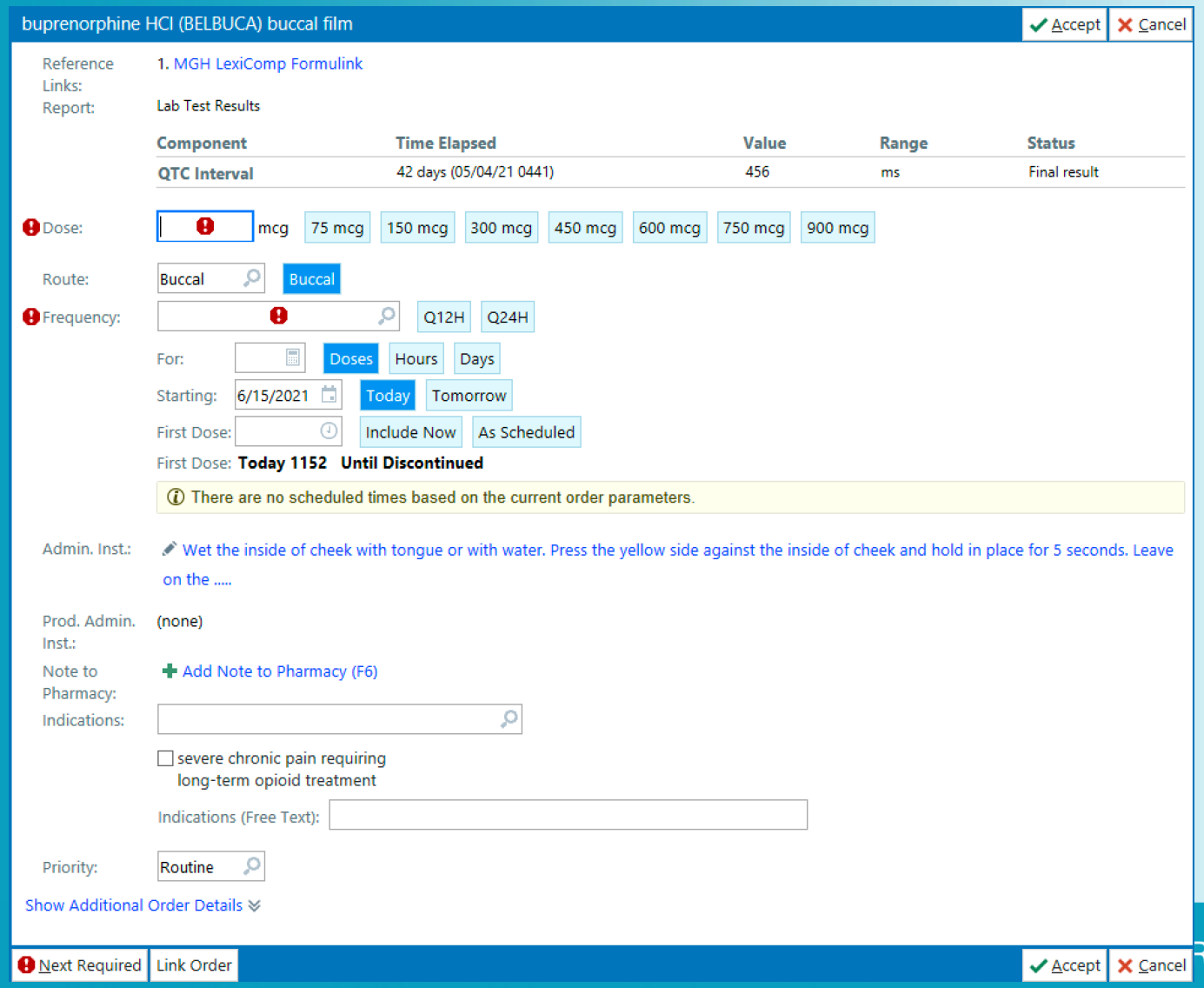
Belbuca® buccal film doses

FDA approved for chronic pain



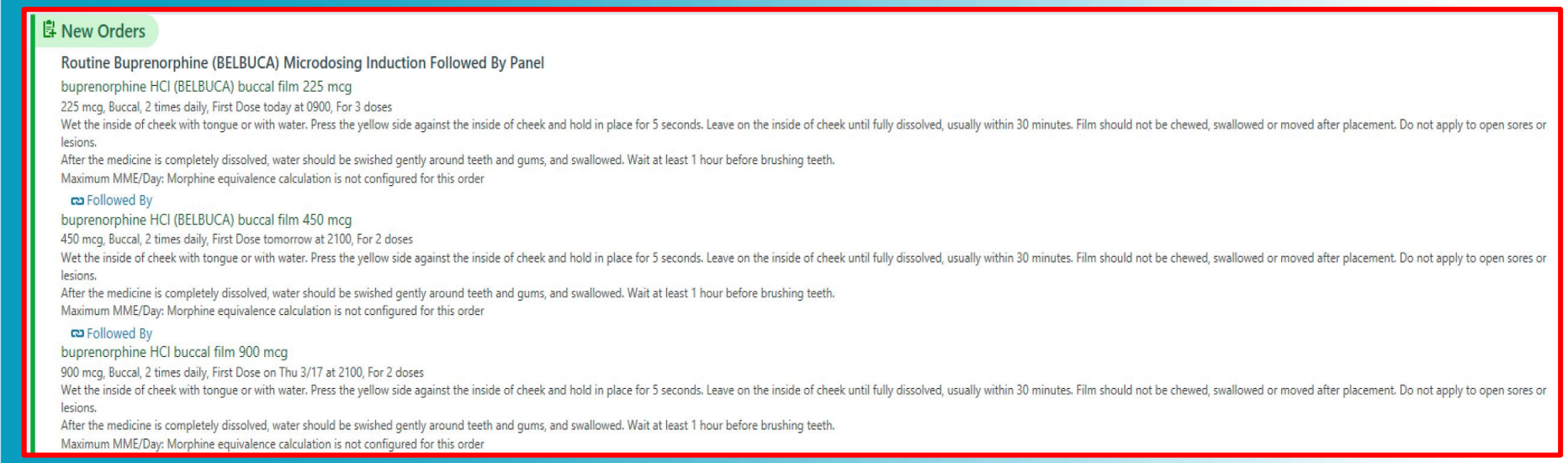
Belbuca:Suboxone bioequivalence

75mcg	≈	0.167mg
150mcg	≈	0.334mg
300mcg	≈	0.668mg
450mcg	≈	1.0mg
600mcg	≈	1.336mg
750mcg	≈	1.67mg
900mcg	≈	2.0mg

MGH low dose buprenorphine (Belbuca®) order set

1. Modified Bernese method

2. Rapid method



New Orders

Routine Buprenorphine (BELBUCA) Microdosing Induction Followed By Panel

buprenorphine HCl (BELBUCA) buccal film 225 mcg

225 mcg, Buccal, 2 times daily, First Dose today at 0900, For 3 doses

Wet the inside of cheek with tongue or with water. Press the yellow side against the inside of cheek and hold in place for 5 seconds. Leave on the inside of cheek until fully dissolved, usually within 30 minutes. Film should not be chewed, swallowed or moved after placement. Do not apply to open sores or lesions.

After the medicine is completely dissolved, water should be swished gently around teeth and gums, and swallowed. Wait at least 1 hour before brushing teeth.

Maximum MME/Day: Morphine equivalence calculation is not configured for this order

Followed By

buprenorphine HCl (BELBUCA) buccal film 450 mcg

450 mcg, Buccal, 2 times daily, First Dose tomorrow at 2100, For 2 doses

Wet the inside of cheek with tongue or with water. Press the yellow side against the inside of cheek and hold in place for 5 seconds. Leave on the inside of cheek until fully dissolved, usually within 30 minutes. Film should not be chewed, swallowed or moved after placement. Do not apply to open sores or lesions.

After the medicine is completely dissolved, water should be swished gently around teeth and gums, and swallowed. Wait at least 1 hour before brushing teeth.

Maximum MME/Day: Morphine equivalence calculation is not configured for this order

Followed By

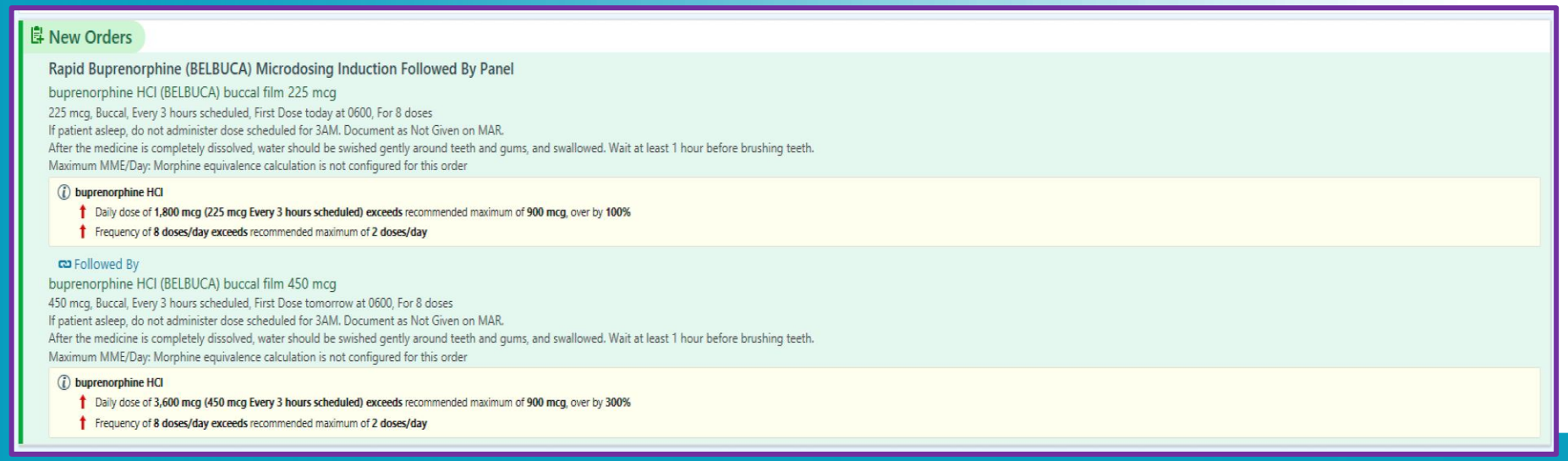
buprenorphine HCl buccal film 900 mcg

900 mcg, Buccal, 2 times daily, First Dose on Thu 3/17 at 2100, For 2 doses

Wet the inside of cheek with tongue or with water. Press the yellow side against the inside of cheek and hold in place for 5 seconds. Leave on the inside of cheek until fully dissolved, usually within 30 minutes. Film should not be chewed, swallowed or moved after placement. Do not apply to open sores or lesions.

After the medicine is completely dissolved, water should be swished gently around teeth and gums, and swallowed. Wait at least 1 hour before brushing teeth.

Maximum MME/Day: Morphine equivalence calculation is not configured for this order



New Orders

Rapid Buprenorphine (BELBUCA) Microdosing Induction Followed By Panel

buprenorphine HCl (BELBUCA) buccal film 225 mcg

225 mcg, Buccal, Every 3 hours scheduled, First Dose today at 0600, For 8 doses

If patient asleep, do not administer dose scheduled for 3AM. Document as Not Given on MAR.

After the medicine is completely dissolved, water should be swished gently around teeth and gums, and swallowed. Wait at least 1 hour before brushing teeth.

Maximum MME/Day: Morphine equivalence calculation is not configured for this order

buprenorphine HCl

Daily dose of **1,800 mcg (225 mcg Every 3 hours scheduled) exceeds** recommended maximum of **900 mcg**, over by **100%**

Frequency of **8 doses/day exceeds** recommended maximum of **2 doses/day**

Followed By

buprenorphine HCl (BELBUCA) buccal film 450 mcg

450 mcg, Buccal, Every 3 hours scheduled, First Dose tomorrow at 0600, For 8 doses

If patient asleep, do not administer dose scheduled for 3AM. Document as Not Given on MAR.

After the medicine is completely dissolved, water should be swished gently around teeth and gums, and swallowed. Wait at least 1 hour before brushing teeth.

Maximum MME/Day: Morphine equivalence calculation is not configured for this order

buprenorphine HCl

Daily dose of **3,600 mcg (450 mcg Every 3 hours scheduled) exceeds** recommended maximum of **900 mcg**, over by **300%**

Frequency of **8 doses/day exceeds** recommended maximum of **2 doses/day**

PSYCHIATRY ACADEMY

- **Belbuca® FDA-approved for chronic pain**
- **Belbuca® 225mcg ≈ Suboxone® 0.5mg**
- **Belbuca® PK/peak concentrations 2.5-3 hours**
- **Full opioid agonists discontinued on last day of induction**
- **Suboxone initiated on first day post induction**

Weimer. Hospital-based buprenorphine micro-dose initiation. *J of Addiction Medicine,* September 2020.

Complicated low dose buprenorphine initiation: pregnancy

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

24-year-old female 31-week partum, complex psychiatric history (anxiety, MDD, PTSD, borderline personality d/o), severe OUD (previously on ER-BUP, partum methadone) a/f methadone stabilization. Her methadone was up-titrated to 98mg in the morning and 90mg in the evenings. Unfortunately, hospital course c/b premature rupture, underwent urgent c-section on HD #23.

She noted prior success on Suboxone and wanted to restart. She underwent a **Hybrid Belbuca micro-dose/Subutek low dose induction** to therapeutic buprenorphine from a total daily methadone of 188mg.

HD #26 started **Belbuca 75mcg** (**≈0.167mg** Subutek) Q4 for 2 doses, 150mcg (**≈0.334mg**) Q4 for 2 doses, 300mcg (≈0.668mg) Q4 for 2 doses, 450mcg (≈1mg) BID for 2 doses, Subutex 2mg BID for 2 doses, Subutek 4mg BID (methadone 78/70mg discontinued) for 2 doses then Subutek 8mg BID

Induction protocol lasted 6 days. No subjective withdrawal symptoms.

She was discharged to Special Care Nursery HD #32. **She received Sublocade in the Bridge Clinic on HD #33**.

She continues to follow-up with our HOPE clinic, ongoing psychosocial stressors. She continues to receive Sublocade.

Complicated low dose buprenorphine initiation: pregnancy

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

32-year-old female 23-week partum (followed by MGH HOPE clinic), known abnormal fetal survey, severe fentanyl use disorder (124mg daily for the past 8 years), ongoing injection fentanyl use (1-2x/week) admitted for transition from methadone to buprenorphine-naloxone. She wanted to transition to SL buprenorphine and eventually ER buprenorphine. She started buprenorphine 0.5mg daily for two days. She was admitted to antepartum unit on day #3. She continued buprenorphine 1mg BID for two days.

HD #3 received 2mg once and had minimal withdrawal symptoms (10% methadone decrease to 110mg on HD #2), included sweating, mydriasis, restlessness and anxiety. Symptoms managed effectively with low dose clonazepam and clonidine.

She was transitioned to **Belbuca 750mcg BID** (≈1.67mg Suboxone) for one dose, 900mcg (≈2mg Suboxone) BID for two doses. Suboxone 4mg BID for three dose then 6mg BID. Methadone discontinued on HD #5. She was discharged on Suboxone 6mg BID.

Total induction-transition to therapeutic buprenorphine duration was 9 days, including 7 days in the hospital.

She was discharged and continues to follow-up with our HOPE clinic, currently on Suboxone 6mg morning and 8mg evenings. No fentanyl use in the past month. She notes avoidance of OTP area, which was triggering.

MGH low dose induction experiences/observations

- Concern for precipitated withdrawal
  - occurs with cross-titration to higher standard buprenorphine doses (≥8mg)
  - usually mild-moderate severity
  - severity lower than standard buprenorphine induction
  - risk likely higher in patients stabilized on intra-hospital high dose long-acting full agonist opioids (e.g., methadone)
  - subgroup represents a population that need initial smaller doses of buprenorphine at extended dosing intervals
  - avoid tapering of high dose methadone (risk for withdrawal, unclear if methadone or buprenorphine

- Treatment
  - buprenorphine (high-dose) macro-induction[1,2]
  - large doses, short inter-dose intervals (1-4 hours), total 12-32mg dose[1]

[1] Herring. High-Dose Buprenorphine Induction in the Emergency Department for Treatment of Opioid Use Disorder. *JAMA Netw Open.* 2021. [2] Oakley et al. Managing opioid withdrawal precipitated by buprenorphine with buprenorphine. *Drug and Alcohol Review*. 2021.

Our lessons learned to date…

PSYCHIATRY ACADEMY

Buprenorphine's unique pharmacokinetics

- multimodal functionality at mOR; high affinity, low dissociative, competitive agonist
- favorable safety profile
- effective bridge tool; overlap full agonist opioids to buprenorphine
- discriminates b/w physical and psychological pain (effective method to taper off full agonist opioids)
- Belbuca doses, 75mcg ≈ 0.2mg buprenorphine, allows versatile **microdosing** use
- **different approach to patients on high-dose intra-hospital methadone with dependence**

Evidence based literature lacking but common themes

- low doses, short inter-dose intervals, can continue/taper or discontinue full opioid agonists
- OUD (with acute pain) or chronic opioid dependence
- multiple patient settings
- non-standardized report of no/mild w/d, likely most patients will have mild w/d

Limited conclusions

- optimal dosing, effectiveness, safety, patient subgroups/clinical settings to optimize benefits

Patient centric

- **patient comfort, agency, autonomy**; <u>long-term engagement with buprenorphine MOUD</u>

Low dose buprenorphine initia

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Guiding principles

1. Chose the appropriate clinical situation
   - Current opioid treatment for acute or chronic pain, current methadone treatment (maintenance or intra-hospital dependence), opioid withdrawal intolerance, high potency synthetic opioid use (e.g., fentanyl)
2. Initiate at a low buprenorphine dose
3. Titrate buprenorphine dose gradually
4. Continue full opioid agonist, even if nonmedical
5. Communicate explicitly with frequent monitoring (e.g., human touchs)
   - shared-decision making, autonomy, higher rates of treatment engagement/retention
6. Pause or delay buprenorphine dose changes if opioid withdrawal symptoms
7. Buprenorphine is LIFE-SAVING amidst historic synthetic opioid overdose deaths, especially in individuals of color

Additional slides

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Clinical definitions

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Low dose buprenorphine initiation

Method of buprenorphine initiation, steps include;

- Bernese method[1]
- Low doses of buprenorphine formulations
- Continuation/bridging of full opioid agonists (e.g., oxycodone, heroin, fentanyl, methadone)
- Transition to the therapeutic doses of buprenorphine

discontinuation of full opioid agonists

Complicated buprenorphine initiation[2]

- Standard buprenorphine dosing
- Development of precipitated withdrawal
- Associated with pre-initiation methadone use
- Prior history of buprenorphine use less likely
- Associated with lower 30-day treatment retention

[1] Hämmig et al. Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method. *Subst Abuse Rehabil*. 2016. [2] Whitley et al. Factors Associated with Complicated Buprenorphine Inductions. *Journal of Substance Abuse Treatment* 2010

Dosing guides for outpatient low dose buprenorphine film/tablet initiation

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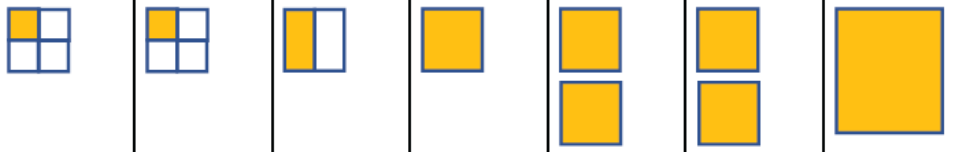
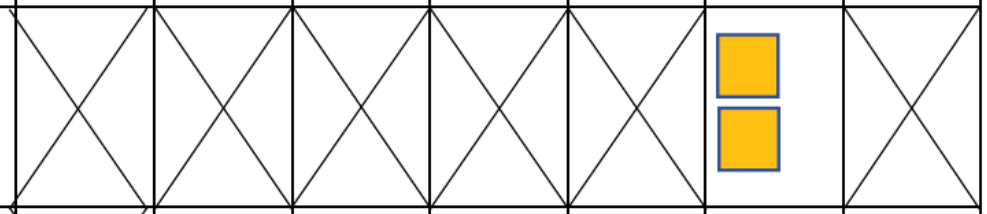
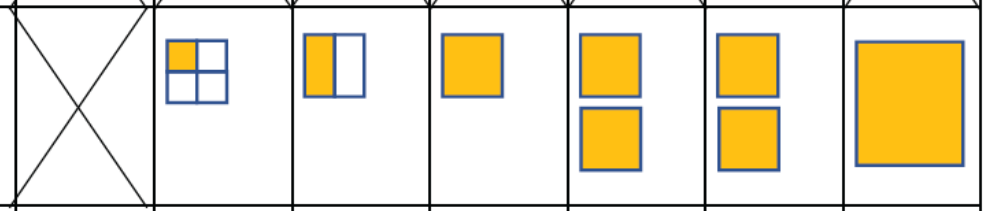
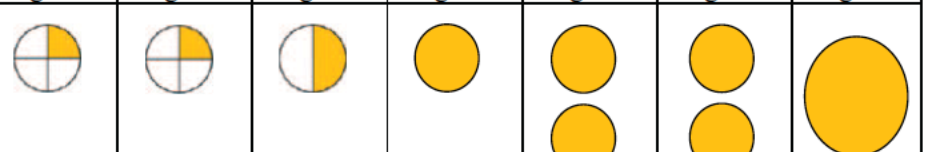
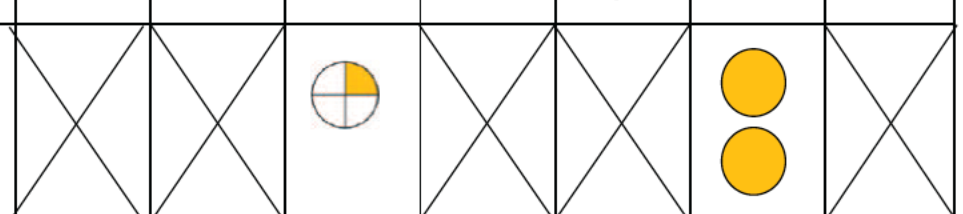
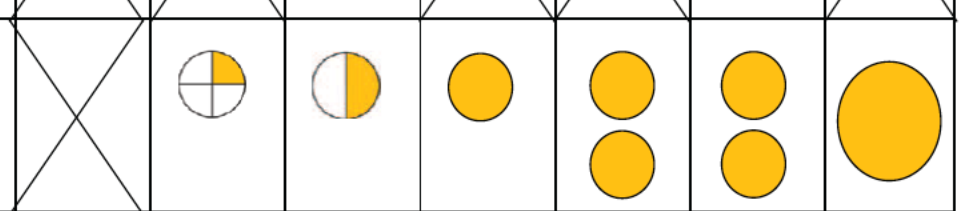
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Buprenorphine dose	0.5mg daily	0.5mg BID	1mg BID	2mg BID	4mg BID	4mg TID	8mg BID
Film size	2mg	2mg	2mg	2mg	2mg	2mg	8mg
Morning dose							
Afternoon Dose							
Night dose							
Full agonist	Continue	Continue	Continue	Continue	Continue	Continue	STOP

BID=twice per day
TID=Three times per day

A Dosing Guide for an example low dose initiation regimen

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

BID=twice per day
TID=Three times per day

B Dosing Guide for an example blister pack regimen

Cohen et al. Low Dose Initiation of Buprenorphine: A Narrative Review and Practical Approach. J Addict Med. 2021. Epub ahead of print.

Low-dose buprenorphine initiation protocol using 24° 20 mcg buprenorphine transdermal patch

TABLE 4. Low-Dose Buprenorphine Initiation Protocol

A. Standard Protocol

Initiation Day	Dosing Schedule	Notes
1	20 mcg buprenorphine transdermal patch × 24 hours	Patch on × 7 days
2	patch + 1 mg SL bup/nx twice daily	
3	patch + 2 mg SL bup/nx twice daily	
4	patch + 4 mg SL bup/nx twice daily	
5	patch + 6 mg SL bup/nx twice daily	
6	patch + 8 mg SL bup/nx twice daily	
7	increase bup/nx as needed NTE 24 mg/24 hours*	Remove patch

B. Acute pain protocol

Initiation Day	Dosing Schedule	Notes
1	20 mcg buprenorphine transdermal patch × 24 hours	Patch on × 7 days
2	patch + 1 mg SL bup/nx twice daily	
3	patch + 1 mg SL bup/nx three times daily	
4	patch + 2 mg SL bup/nx three times daily	
5	patch + 4 mg SL bup/nx three times daily	Begin full opioid agonist taper‡
6	increase bup/nx as needed for pain NTE 24 mg/24 hours†	
7		Remove patch

C. Transition from Methadone protocol

Initiation Day	Dosing Schedule	Notes
1	20 mcg buprenorphine transdermal patch × 24 hours	Patch on × 7 days; Continue methadone§
2	20 mcg buprenorphine transdermal patch × 24 hours	No SL bup/nx; Continue methadone
3	patch + 1 mg SL bup/nx × 1 dose	Continue methadone vs. start methadone taper based on patient preference¶
4	patch + 1 mg SL bup/nx twice daily	
5	patch + 2 mg SL bup/nx twice daily	
6	patch + 3 mg SL bup/nx twice daily	
7	4 mg SL bup/nx twice daily	Remove patch
8	5 mg SL bup/nx twice daily	
9	6 mg SL bup/nx twice daily	
10	8 mg SL bup/nx twice daily	Stop methadone
11	increase bup/nx as needed NTE 24 mg/24 hours*	

*Final dose dependent on patient need and based on medical assessment.
†Final dose dependent on patient need and based on medical assessment in split dosing.
‡Taper schedule dependent on individual patient case and medical assessment.
§Low-dose buprenorphine initiation should be started once methadone dose 80 mg or less.
¶We find patient input on this decision supports success.
bup/nx indicates buprenorphine/naloxone either tablet or film; NTE, not to exceed; SL sublingual

Button et al. Low-dose Buprenorphine Initiation in Hospitalized Adults with Opioid Use Disorder: A Retrospective Cohort Analysis. *J Addiction Med*. 2022.

Oregon Health & Science University Retrospective case series – low dose buprenorphine initiation in hospitalized patients

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.

TABLE 1. Characteristic of Participants Undergoing Low-dose Buprenorphine Initiation

Participant Characteristic	n (%)
Unique individuals[*]	68
Age – mean (SD)	45 (13.6)
Gender (male)	41 (60.3)
Race	
White	64 (95.6)
Multiracial	1 (1.5)
Asian	1 (1.5)
Not recorded	1 (1.5)
Ethnicity	
Not Hispanic or Latino	64 (94.1)
Hispanic	3 (4.4)
Not recorded	1 (1.5)
Insurance type	
Medicare	1 (2.9)
Medicaid	53 (78.0)
Other	13 (19.1)
Houseless	24 (35.3)
Admission diagnosis type	
Infection	39 (57.3)
Trauma	11 (16.2)
Cardiovascular disease	4 (5.9)
Other	14 (20.5)
Substance use disorder type[†]	
Opioid	63 (92.6)
Amphetamine	36 (52.9)
Alcohol	9 (13.2)
Benzodiazepine	7 (10.3)
Cocaine	5 (7.4)
Mental health diagnosis	36 (52.9)
Prior buprenorphine prescription	39 (57.4)
Morphine milligram equivalents administered 24 hours before low-dose initiation – mean (SD)[‡]	198 (98.3)
Total hospital length of stay – mean (SD)	24 (19.2)

[*]Three individuals underwent more than one low-dose initiation.
[†]Not mutually exclusive.
[‡]Data missing for six low-dose initiations.

Button et al. Low-dose Buprenorphine Initiation in Hospitalized Adults with Opioid Use Disorder: A Retrospective Cohort Analysis. *J Addiction Med*. 2022.