

Starting Buprenorphine in the Fentanyl Era: Is Low-dose Initiation (“Microdosing”) the Solution?

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Disclosures

- Devang Gandhi: No relevant disclosures
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Learning Objectives

Participants in this activity will learn about:

1. The challenges of initiating buprenorphine in patients using opioids with a long duration of action such as fentanyl or methadone.
2. Pharmacological rationale and differences between conventional vs low-dose buprenorphine initiation
3. Some buprenorphine “micro-dosing” protocols and evidence to support their use.

Terminology

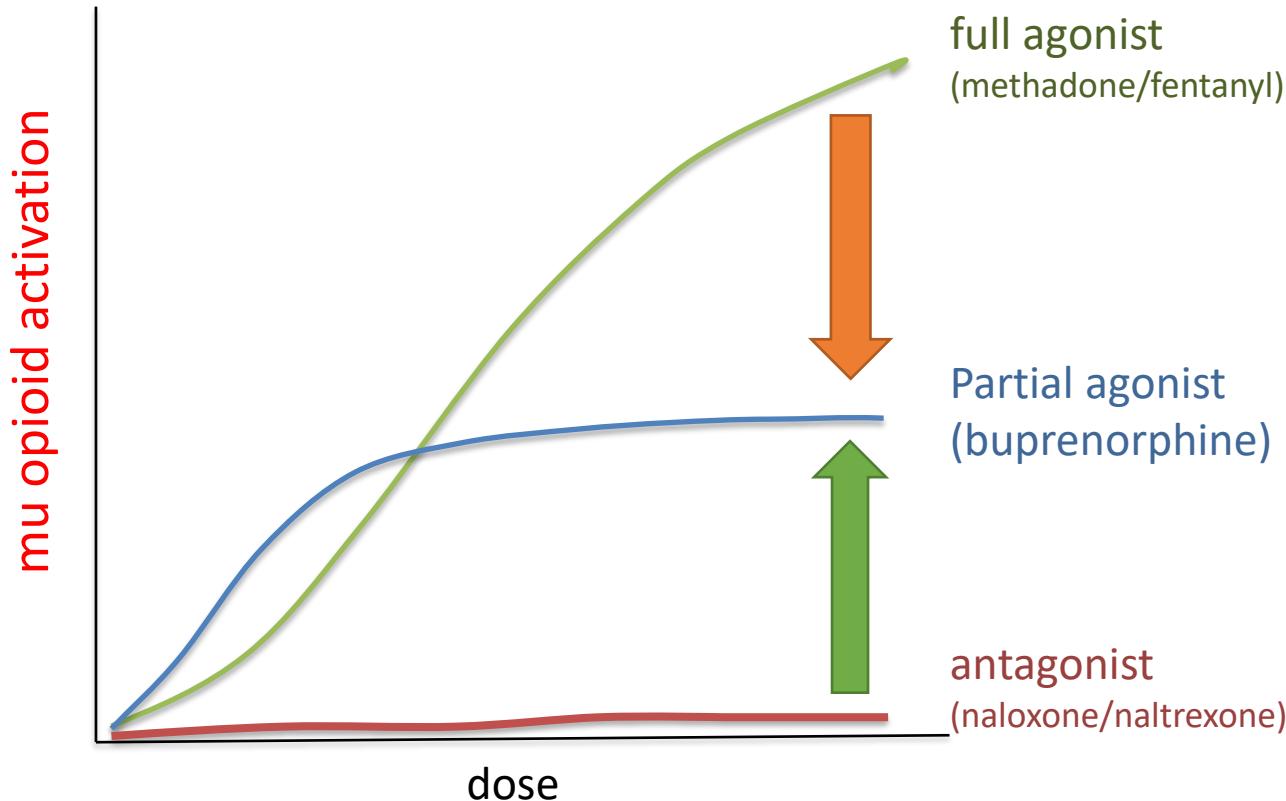
- Micro-dosing or micro-induction: commonly used but misleading; micro-dosing also applied to the use of very small doses of psychedelics (e.g., psilocybin mushrooms)
- “Bernese method”: Initiation of buprenorphine overlapped with ongoing use of heroin/full agonist; many variations of this protocol are now in use
- Rapid/Ultra-rapid Microdosing: shorter initiation protocols of 1-5 days
- Low Dose Buprenorphine Initiation (LDBI): Now favored as a general term that captures the wide variety of protocols being used

Case Vignette

- 50yow, employed, w/ OUD, on methadone maintenance for 2 years
- Daily dose 50mg, still using non-rx opioids (fentanyl + heroin), requested to switch to buprenorphine due to constipation and feeling drowsy at work
- Tapered down to methadone 9mg/d over a month, asked to skip the dose for 2 days and report back to initiate buprenorphine
- Missed the appt and used 2 films of 8mg bup she got from a friend to alleviate withdrawal
- Experienced severe opioid withdrawal and was taken to the ER where she received 10mg methadone before being discharged
- Came to the methadone program right after due to continuing withdrawal requesting to revert to methadone tx and was restarted w/ 30mg methadone
- Withdrawal diminished, but continued for another couple of days
- Now back on methadone 65mg daily, doing well

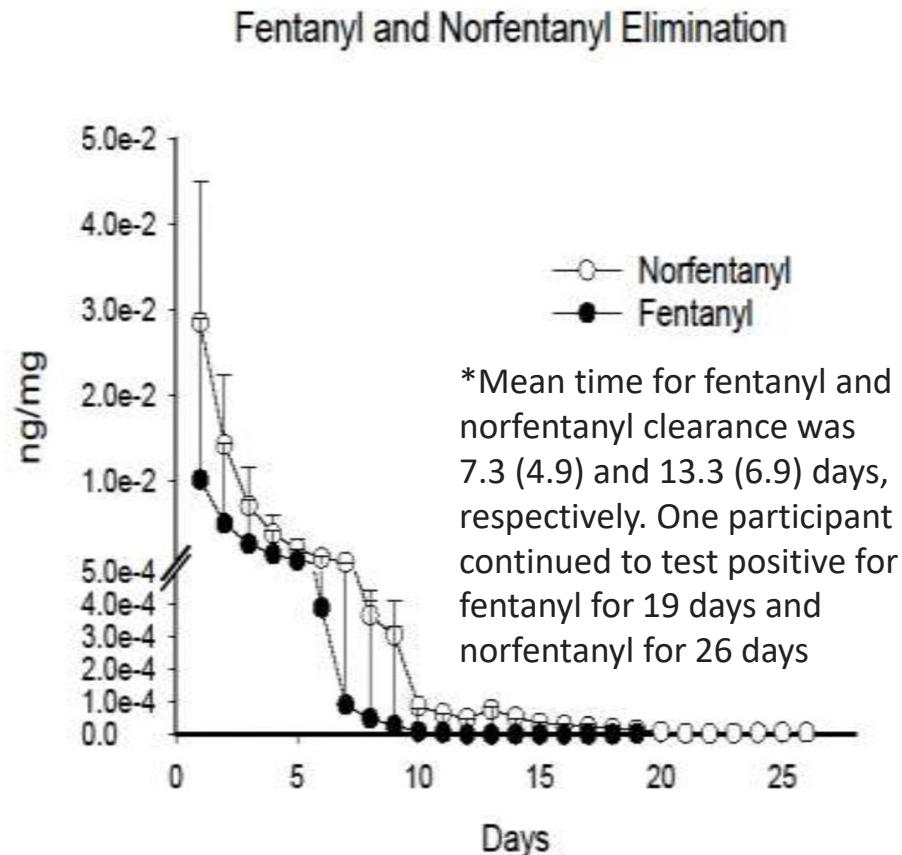
Why Do We Need LDBI?

- Initiation of buprenorphine presents considerable challenges due to the risk of precipitated withdrawal (PW)
- Particularly true when transitioning from full mu opioid receptor (MOR) agonists with prolonged action (e.g., methadone/fentanyl) to buprenorphine
- PW occurs because of buprenorphine's low intrinsic activity (i.e., ***partial agonist*** action) at the MOR, combined with its capacity to displace full agonists from the MOR (i.e., ***high affinity***)



Fentanyl Pharmacology

- Distinct pharmacological profile vs other opioids
 - high potency (100x morphine)
 - high lipophilicity
 - sequestration and gradual release from lipid tissue
 - extended elimination half-life*
 - long window of risk for PW



*Huhn AS, Hobelmann JG, Oyler GA, Strain EC. Protracted renal clearance of fentanyl in persons with opioid use disorder. *Drug Alcohol Depend*. 2020 Sep 1;214:108147. doi: 10.1016/j.drugalcdep.2020.108147. PMID: 32650192; PMCID: PMC7594258.

MOR Signaling

G-Protein
Analgesia

Morphine

Fentanyl

Beta-arrestin
Respiratory depression

The Usual Approach to PW

- Existing guidelines focus primarily on methadone to buprenorphine transitions and recommend tapering methadone to less than 30mg, discontinuing it for 1-2 days and then starting buprenorphine at a low dose (2mg SL)*
- Many patients experience PW even after following the recommended protocol
- PW has emerged as a major issue in routine practice since non-pharmaceutical fentanyl became the default opioid sold on the street

*Substance Abuse and Mental Health Services Administration. *Medications for Opioid Use Disorder*. Treatment Improvement Protocol (TIP) Series 63 Publication No. PEP21-02-01-002. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2021.

Managing Precipitated Withdrawal

- PW risk is traditionally managed by:
 - tapering and stopping the long-acting full-agonist opioid first
 - a longer interval between last full-agonist opioid use and 1st buprenorphine dose
 - waiting to start bup till patient evidences greater intensity of withdrawal (e.g., higher COWS score)
 - managing PW using symptom-based treatment
 - all with the attendant risks of withdrawal, treatment drop-out, relapse or overdose
- LDBI offers an alternative way to reduce the risk of PW by initiating bup using smaller (“micro”) doses without first tapering/stopping the full agonist opioid

What is Low-dose Buprenorphine Initiation?*

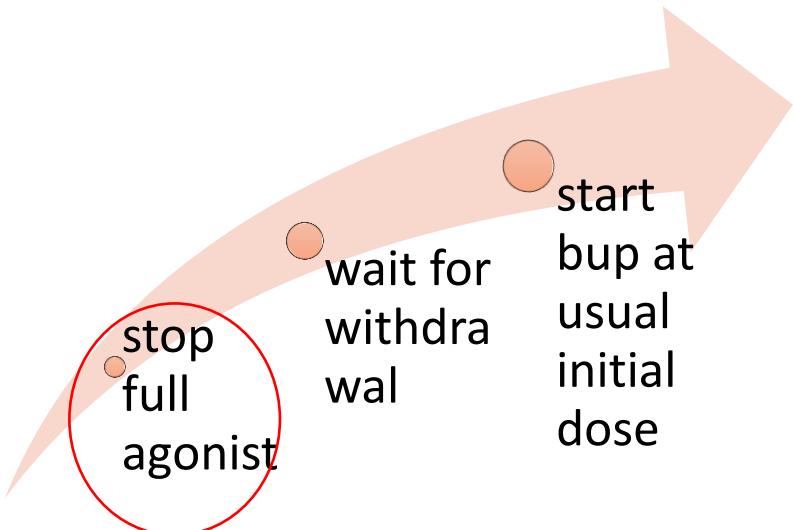
- LDBI “is a novel approach that, by harnessing buprenorphine’s unique pharmacological profile, may allow circumventing the need for prolonged opioid tapers, and reduce the risk of precipitated withdrawal.”
- In contrast to traditional initiation, patients may continue their use of full opioid agonists (e.g., methadone or fentanyl) until a therapeutic dose of buprenorphine has been achieved. At that point, the full opioid agonist is discontinued, without the need for a slow taper.
- Typically, this process takes place over a 3- to 10-day period, however, time frames of as long as 1 month have been reported**.

*De Aquino JP, Parida , Sofuoglu M. The Pharmacology of Buprenorphine Microinduction for Opioid Use Disorder. *Clin Drug Investig*. 2021 May;41(5):425-436. doi: 10.1007/s40261-021-01032-7.

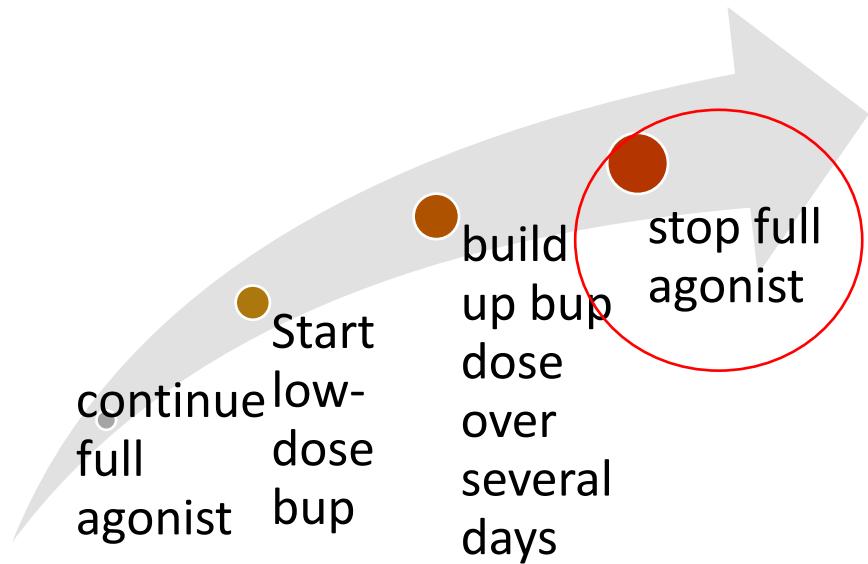
** Cohen et al. Low Dose Initiation of Buprenorphine: A Narrative Review and Practical Approach. *J Addict Med* 2021 Nov. doi: 10.1097/ADM.0000000000000945

Conventional vs LDBI Approach

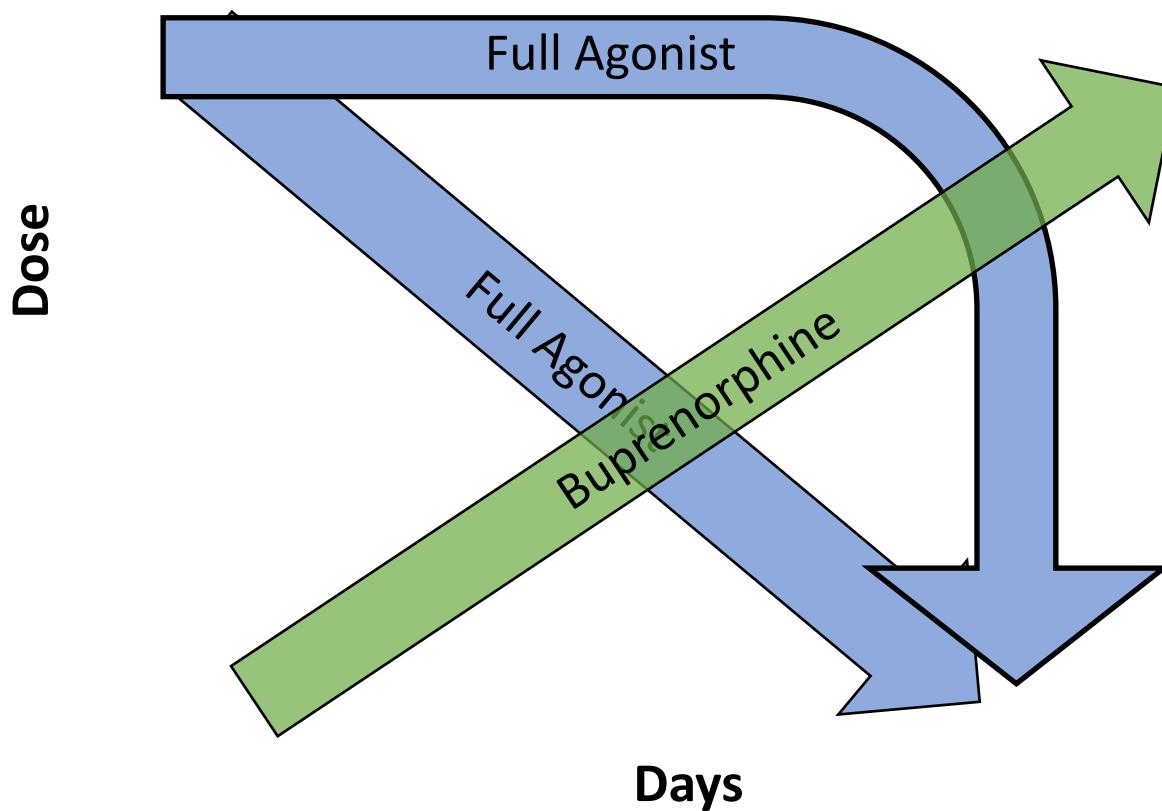
Conventional



Low-dose Initiation



Essentially



The goal is to gradually sneak buprenorphine on to the mu receptors, avoiding a catastrophic displacement of the full-agonist all at once which would trigger precipitated withdrawal

“The Bernese Method”*

- Hämmig et al published case reports in German (2010) and English (2016) describing what they called “The Bernese Method” to switch patients from full-agonist opioids to buprenorphine
- Based on several clinical observations:
 - Between 40% and 60% of buprenorphine-maintained persons concomitantly use full μ -receptor agonists and this use is not associated with opioid withdrawal
 - Repetitive administration of the μ -antagonist naloxone quickly leads to a maximum of withdrawal symptoms which then decline despite continued naloxone application, a method used in the 1980s to develop several rapid withdrawal protocols
 - A very small dose of 0.2mg buprenorphine intravenous (iv) did not produce opioid withdrawal in individuals receiving methadone maintenance

*Hämmig R, Kemter A, Strasser J, von Bardeleben U, Gugger B, Walter M, Dürsteler KM, Vogel M. Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method. *Subst Abuse Rehabil.* 2016 Jul 20;7:99-105.

Hypotheses Supporting LDBI

- 1) Repetitive administration of very small buprenorphine doses with sufficient dosing intervals (e.g., 12 hours) should not precipitate opioid withdrawal
- 2) Because of the long receptor binding time, buprenorphine will accumulate at the receptor
- 3) Over time, an increasing amount of the full μ -agonist will be replaced by buprenorphine at the opioid receptor.

Original Bernese Case*

- Patient experienced prolonged withdrawal using conventional approach
- She was then started on a small dose (0.2mg SL) of bup with overlapping heroin use, and gradual daily increases in bup dose, till pt successfully reached a maintenance dose
- Later this patient also switched to from bup to naltrexone using a similar approach starting with very small doses of naltrexone and gradually increasing to a maintenance dose of 25mg daily, overlapping with 2mg buprenorphine for several days

*Hämmig R, Kemter A, Strasser J, von Bardeleben U, Gugger B, Walter M, Dürsteler KM, Vogel M. Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method. *Subst Abuse Rehabil.* 2016 Jul 20;7:99-105.

Bernese Protocol*

Table I Buprenorphine dosing and use of street heroin in case I

Day	Buprenorphine (sl)	Street heroin (sniffed)
1	0.2 mg	2.5 g
2	0.2 mg	2 g
3	0.8+2 mg	0.5 g
4	2+2.5 mg	1.5 g
5	2.5+2.5 mg	0.5 g
6	2.5+4 mg	0
7	4+4 mg	0
8	4+4 mg	0
9	8+4 mg	0

Abbreviation: sl, sublingual.

Evidence Base for LDBI

- Low quality: Limited to case reports and case series, 2 reviews
- An RCT underway in Canada
- Case reports indicate this could be an effective approach to reduce the risk of precipitated withdrawal
- A variety of protocols have been used with initial buprenorphine doses ranging between 0.2mg and 1 mg (SL)
- Transdermal buprenorphine in doses about 5-20 mcg/h has also been used
- Typical dose escalation to therapeutic levels over 5-7 days while continuing the full agonist, then discontinuing it

LDBI Review*

- Moe et al (2021) Found 20 case reports/series covering 57 cases, 75% published between 2019-2020
- Starting doses ranged from 0.03 to 1.0 mg (median 0.5 mg)
- Maintenance doses ranged from 8 to 32 mg
- Among 57 patients described, 26 had an overlapping opioid prescribed, the others used non-rx opioids during induction
- 9 patients were on rx methadone, 5 on fentanyl, 5 on hydromorphone, 3 on morphine, 4 on multiple opioids
- All patients achieved maintenance dose of buprenorphine

Moe J, O'Sullivan F, Hohl CM, Doyle-Waters MM, Ronsley C, Cho R, Liu Q, Azar P. Short communication: Systematic review on effectiveness of micro-induction approaches to buprenorphine initiation. *Addict Behav.* 2021 Mar;114:106740. doi: 10.1016/j.addbeh.2020.106740.

Precipitated Withdrawal During LDBI*

- Precipitated withdrawal occurred in 3/57 patients- all in patients transitioning from methadone
- For these cases, the median buprenorphine starting dose was 0.40 mg, median duration 6 days, median maintenance dose 12 mg, and mean rate of dose change to 8 mg was 1.17 mg/day (SD: 0.11).
- Among studies not reporting precipitated withdrawal, the median starting dose was 0.50 mg, median duration 6 days, median maintenance dose 16 mg, and mean rate of dose change to 8 mg was 1.36 mg/day (SD: 0.41)
- Median doses (and corresponding MME) of overlapping methadone among patients experiencing precipitated withdrawal were 20-30 mg (median MME 70 mg)

Some Cautions

- LDBI has not yet been definitively been shown to be more effective than the conventional approach, though it seems safe and promising
- There are many different protocols and we do not yet know which one is the most optimal
- Dosing remains challenging in the absence of low dose SL buprenorphine formulations
- Adapt your approach to the individual patient, rather than just following a protocol
- Do consider seeking a consultation if you are not sure how to proceed

Example: Outpatient LDBI Protocol*

Table 2. Outpatient Microinduction Protocol Using Sublingual 2 mg Buprenorphine/Naloxone Tablets or Films

Day	Bup/Nlx Dose and Frequency	Full Agonist Opioid
1	0.5 mg daily (1/4 tablet or film)	No change
2	0.5 mg BID	No change
3	1 mg BID (half-tablet or film)	No change
4	2 mg BID	No change
5	2 mg TID	No change
6	4 mg TID	No change
7 and beyond	Per provider discretion	Taper by 25% weekly

Bup, Buprenorphine; Nlx, naloxone; BID, twice a day; TID, twice a day.

Robbins JL, Englander H, Gregg J. Buprenorphine Microdose Induction for the Management of Prescription Opioid Dependence. J Am Board Fam Med. 2021 Feb;34(Suppl):S141-S146.

Sample LDBI Protocol

- Designed by Ashish Thakrar, MD (apthakrar@pennmedicine.upenn.edu)
- Not formally studied or published
- Case series suggest this protocol is effective for methadone doses \leq 40mg; only a few reports for 75-100mg
- For patients on methadone through an Outpatient Treatment Program, coordinate care with the OTP.

Day	Buprenorphine dose	How much of a strip for each dose?	Street opioids or methadone
1	0.5mg SL once daily	Quarter of a 2mg strip	Continue
2	0.5mg SL twice daily	Quarter of a 2mg strip	Continue
3	1mg SL twice daily	Half of a 2mg strip	Continue
4	2mg SL twice daily	Full 2mg strip	Continue
5	4mg SL twice daily	Half 8mg strip	Continue
6	8mg SL twice daily	Full 8mg strip	Stop
7	8mg-12mg SL twice daily	Full 8-12mg strip	Stop

References:

Huhn AS, Hobelmann JG, Oyler GA, Strain EC. Protracted renal clearance of fentanyl in persons with opioid use disorder. *Drug and Alcohol Dependence*. 2020;214:108147. doi:10.1016/j.drugalcdep.2020.108147

Elkader A, Sproule B. Buprenorphine: Clinical pharmacokinetics in the treatment of opioid dependence. *Clinical Pharmacokinetics*. 2005 Jul;44(7):661-80.

Ghosh SM, Klaire S, Tanguay R, Manek M, Azar P. 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. *Canadian Journal of Addiction*. 2019;10(4):41-50. doi:10.1097/CXA.0000000000000072

Brar R, Fairbairn N, Sutherland C, Nolan S. Use of a novel prescribing approach for the treatment of opioid use disorder: Buprenorphine/naloxone micro-dosing – a case series. *Drug Alcohol Rev*. 2020 Jul;39(5):588-94.

Terasaki D, Smith C, Calcaterra SL. Transitioning Hospitalized Patients with Opioid Use Disorder from Methadone to Buprenorphine without a Period of Opioid Abstinence Using a Microdosing Protocol. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*. 2019;39(10):1023-9.

Daquino JP, Fairgrieve C, Klaire S, Garcia-Vassallo G. Rapid Transition From Methadone to Buprenorphine Utilizing a Microdosing Protocol in the Outpatient Veteran Affairs Setting. *Journal of Addiction Medicine*. 2020 Sep;14(5):e271-3.

Howard Street LDBI Protocol

- Courtesy of San Francisco Department of Public Health
- The patient decides when to stop street opioid use!
 - Typically decrease Day 4-6, stop by Day 7
- Buprenorphine monoproduct tablets may be easier to cut into quarters, and more stable after being cut, vs. bup-nal tablets
- Consider using the Mono-Product for the entire protocol, as patients may be distressed by the change in appearance of the pills
- Ancillary medications recommended on Day 4 (clonidine, gabapentin, hydroxyzine) with anticipatory counseling

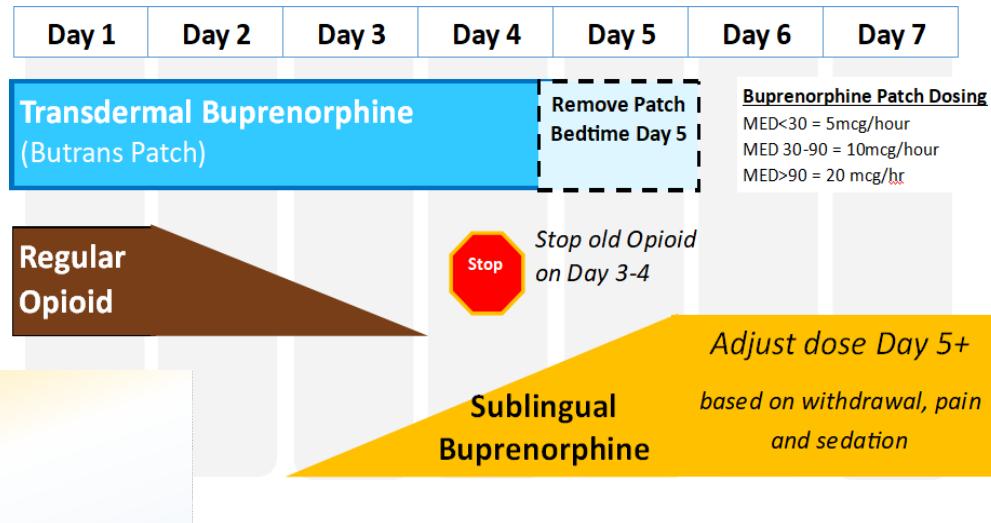
Day	Buprenorphine dose	Splitting instructions
<i>Buprenorphine Mono-Product 2 mg tablets: Blister-pack days 1-3 and dispense #2 tablets</i>		
1	0.5 mg SL of Mono-Product 2 mg tablets	Quarter of a 2mg tablet
2	0.5mg SL twice daily	Quarter of a 2mg tablet
3	0.5 mg SL in the morning, 1 mg SL in the afternoon, 1mg SL in the evening	Quarter of a 2 mg tablet, then half of a 2 mg tablet, then half of a 2 mg tablet
<i>Buprenorphine-Naloxone Product 2mg Tablets: Blister-pack Days 4-6 and dispense #9 tablets</i>		
4	2mg SL twice daily	Full 2mg tablet
5	3mg SL twice daily	One and a half 2mg tablets
6	4mg SL twice daily	Two 4mg tablets
<i>No longer need blister-pack; can change to films if desired</i>		
7	12mg SL in the morning + follow-up with provider to determine dosing	As determined at provider follow up

Butrans Patch to Sublingual Buprenorphine (from opioids like oxycodone, hydrocodone, morphine)

Apply Butrans Patch.
 Remove bedtime on 5th day

Taper Opioid as tolerated
 •Use clonidine as needed
 •Reduce by ~50% Day 2
 •Stop on Day 3 or 4

Start Sublingual Buprenorphine on Day 3 and gradually increase.
 Prescribe buprenorphine/naloxone 2/0.5mg film #30



.Adapted From: Amer Raheemullah, MD; Anna Lembke, MD, JAMA internal medicine. January 2019. Initiating Opioid Agonist Treatment for Opioid Use Disorder in the Inpatient Setting A Teachable Moment
 .Saal D, Lee F. Rapid induction therapy for opioid use disorder using buprenorphine transdermal patch: A case series. Perm J 2020;24:19.124. DOI: <https://doi.org/10.7812/TPP/19.124>
 Webster et al., Understanding Buprenorphine for use in Chronic pain: Expert Opinion. Pain Medicine, 0(0), 2020, 1–10 doi: 10.1093/pmnz356

3 Day Rule: 21CFR

§ 1306.07 Administering or dispensing of narcotic drugs.

(a) A practitioner may administer or dispense directly (but not prescribe) a narcotic drug listed in any schedule to a narcotic dependant person for the purpose of maintenance or detoxification treatment if the practitioner meets both of the following conditions:

- (1) The practitioner is separately registered with DEA as a narcotic treatment program.
- (2) The practitioner is in compliance with DEA regulations regarding treatment qualifications, security, records, and unsupervised use of the drugs pursuant to the Act.

(b) Nothing in this section shall prohibit a physician who is not specifically registered to conduct a narcotic treatment program from administering (but not prescribing) narcotic drugs to a person for the purpose of relieving acute withdrawal symptoms when necessary while arrangements are being made for referral for treatment. Not more than 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.

(c) This section is not intended to impose any limitations on a physician or authorized hospital staff to administer or dispense narcotic drugs in a hospital to maintain or detoxify a person as an incidental adjunct to medical or surgical treatment of conditions other than addiction, or to administer or dispense narcotic drugs to persons with intractable pain in which no relief or cure is possible or none has been found after reasonable efforts.

<https://www.govinfo.gov/app/details/CFR-1998-title21-vol9/CFR-1998-title21-vol9-sec1306-07/summary>

<https://www.ecfr.gov/current/title-21/chapter-II/part-1306/subject-group-ECFR1eb5bb3a23fddo/section-1306.07>

Regulatory Context

- 1974: 3 Day Rule allows for outpatient withdrawal management with “narcotics”
- 2000 Drug Addiction Treatment Act (DATA) authorizes prescription of buprenorphine for opioid dependence
- March 2022: DEA permits dispensing 3-day supply of buprenorphine at a time

X-waiver Regulations

- Under DATA 2000, physicians must complete 8-hour training to obtain an X waiver
- 2016: Comprehensive Addiction and Recovery Act (CARA) extends authority to Nurse Practitioners and Physician Assistants with 24-hour training
- April 2021: Training requirement removed
- Waiver can only be applied to bup products that are FDA-approved for opioid dependence

FDA-approved buprenorphine products for opioid dependence

Type of Buprenorphine Product	Route of Administration	Brand Name
monoproduct, tablet	Sublingual	generic (formerly Subutex)
buprenorphine-naloxone combination product, tablet	Sublingual	generic, Suboxone, Zubsolv
buprenorphine-naloxone, film	Sublingual	Suboxone
monoproduct, injection, extended-release	Subcutaneous	Sublocade
monoproduct, implant	Transdermal	Probuphine

Regulatory Questions for buprenorphine initiation

- How can we utilize bup monoproducts to ease the transition?
 - Transdermal patch (generic, Butrans)
 - Buccal film (Belbuca)
- Both FDA-approved only for chronic pain, not opioid dependence
- Off-label use of any medication is legal
- Must comply with 3-day rule for “narcotics”
 - But transdermal patch has duration of action longer than 3 days
 - No clear answer from DEA on this
- On-label use for pain?
 - And, if clear pain indication, is prescription an option?



Case Vignettes

Case 1: Post-op micro-induction with buccal buprenorphine

26-year-old female w/ PMH of OUD, intravenous substance use, with MSSA infective endocarditis of the tricuspid valve

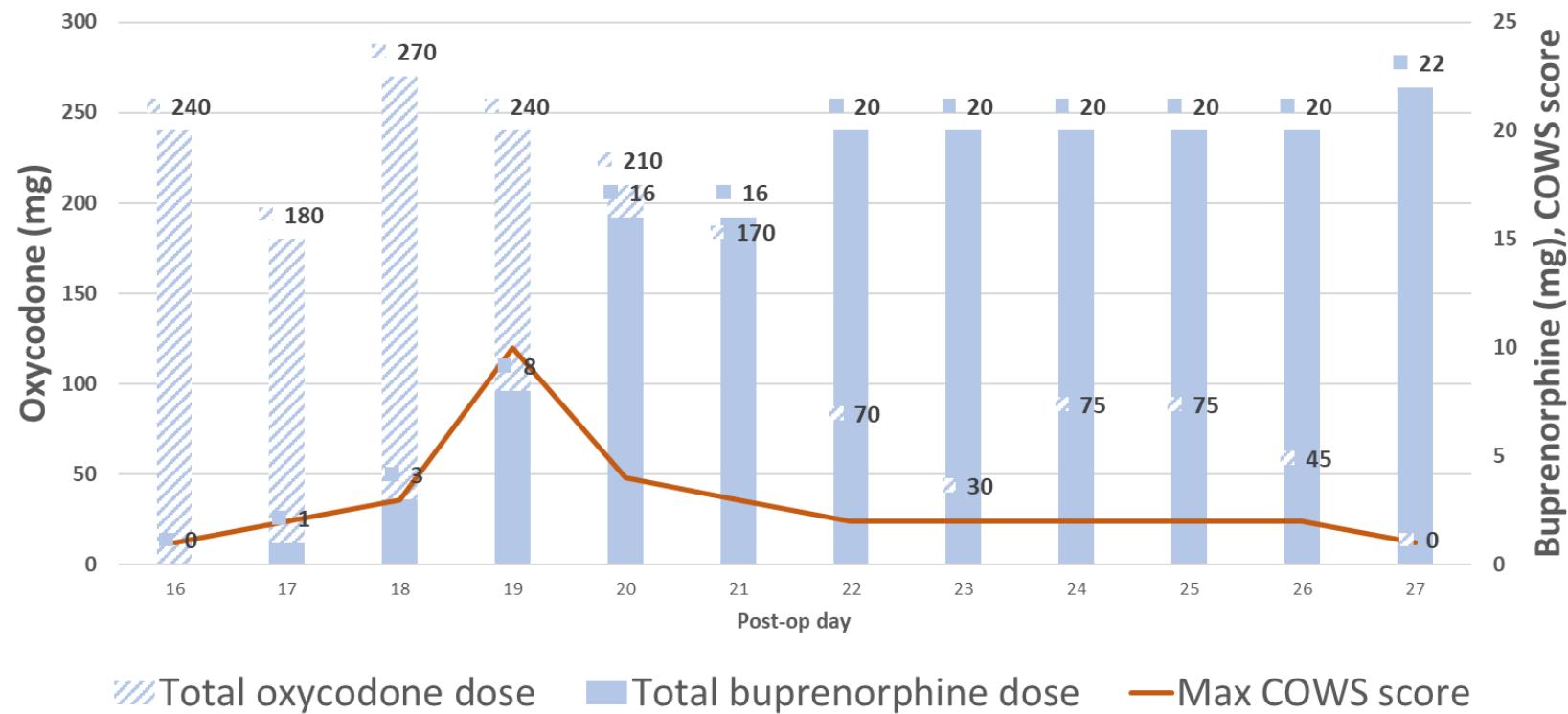
- Fentanyl use prior to admission
- Tricuspid valve reconstruction and dual chamber pacemaker placement
- Post-operative pain
 - Oxycontin 30 mg BID + oxycodone 30 mg q3 prn (6 on average)=240 mg of oxycodone daily
- Discharge barriers
 - Out-of-state insurance, not accepted by PA SARs without suboxone, prolonged QTc

Case 1: Post-op microinduction with buccal buprenorphine

Day	Buprenorphine dose	Full opioid agonist
Day 1	Belbuca 150 mcg q6 hours	Oxycontin 30 mg BID + oxycodone 30 mg q3 hours prn
Day 2	Belbuca 450 mcg q6 hours	Oxycontin 30 mg BID + oxycodone 30 mg q3 hours prn
Day 3	Suboxone 2 mg q6 hours	Oxycontin 30 mg BID + oxycodone 30 mg q3 hours prn
Day 4	Suboxone 4 mg q6 hours	Oxycontin 30 mg BID + oxycodone 30 mg q3 hours prn
Day 5	Suboxone 4 mg q6 hours	Discontinued oxycontin, oxycodone 15 mg q3 prn

Discharged on suboxone 8 mg BID + 4 mg BID without other opioids

Micro-induction: Daily oxycodone doses, buprenorphine doses, and COWS max score by post-op day



Case 2: Microinduction with IV buprenorphine from methadone

64-year-old female w/ PMH of OUD on methadone, HFrEF (15%) s/p AICD, T2DM, COPD on 2L O₂ admitted for CHF exacerbation

- CHF stabilized during medical admission
- Transferred to Chemical Dependency Service for transition to Suboxone from methadone due to her medical comorbidities
- Full opioid agonist was methadone 50 mg, no recent illicit opioid use

Case 2: Microinduction with IV buprenorphine from methadone

Day	Buprenorphine dose	Full opioid agonist
Day 1	Buprenex 0.1 mg q6 hours	Methadone 50 mg
Day 2	Buprenex 0.2 mg q6 hours	Methadone 50 mg
Day 3	Buprenex 0.3 mg q6 hours	Methadone 50 mg
Day 4	Suboxone 2 mg q8 hours	None
Day 5	Suboxone 4 mg q8	None

Discharged on suboxone 8 mg once daily+ 2 mg BID without other opioids

Case 3: Microinduction with IV buprenorphine from methadone

27-year-old female w/ PMH of OUD on methadone, cocaine use disorder, and sickle cell disease with frequent admissions for sickle cell crises admitted for sickle cell pain crisis

- Last used heroin and cocaine 2 days ago, last took methadone 2 days ago
- Difficulty with transportation to methadone clinic, where she has been on a range of 30-80 mg daily depending on her attendance
- Prescribed oxycodone 15 mg QID for chronic pain in addition to methadone
- Collaborated with pain management for plan in hospital

Case 3: Microinduction with IV buprenorphine from methadone

Day	Buprenorphine dose	Full opioid agonist
Day 1	Buprenex 0.1 mg q4 x 2 doses, then Buprenex 0.2 mg q4 x 2 doses, then Buprenex 0.3 mg q4 x 2 doses, then	PCA dilaudid 0.3 mg q10 minutes for breakthrough pain
Day 2-3	Suboxone 2 mg q4 x 2 doses, then Suboxone 4 mg q4 x 6 doses, then Suboxone 8 mg TID	PCA dilaudid 0.3 mg q10 minutes for breakthrough pain
Day 4-6	Suboxone 8 mg TID	PCA dilaudid 0.3 mg q10 minutes for breakthrough pain, then discontinued <i>PCA kept on longer per pain management to ensure pain relief</i>

Discharged on suboxone 8 mg TID (prior auth obtained) + 4 mg BID prn without other opioids

Other variations

- Using oxycodone 10 mg q4 standing for full agonist opioid
- Using Buprenex low doses without full agonist opioid if patient is in some withdrawal (e.g. COWS>8) or per patient preference

Conclusion

- LDBI is a potentially useful approach for initiating buprenorphine in patients on longer-acting full opioid agonists (prescribed or non-prescribed)
- It may help eliminate the need for prolonged opioid taper or abstinence, and reduce the risk of precipitated withdrawal, treatment dropout and relapse/overdose
- Although it has gained a lot of attention and is being applied widely, evidence for its effectiveness is still very preliminary and low-quality, limited to case reports utilizing disparate protocols and transition time-frames
- Urgent need for high-quality RCTs and more LDBI-friendly buprenorphine formulations

Questions?

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