

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

Devang Gandhi, MD

Clinical Professor of Psychiatry

Aaron Greenblatt, MD

Assistant Professor of Psychiatry

Sarah Merritt, MD

MACS Consultant

University of Maryland School of Medicine

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Learning Objectives

Participants in this activity will learn about:

1. The challenge 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 to reduce the risk of precipitated withdrawal.

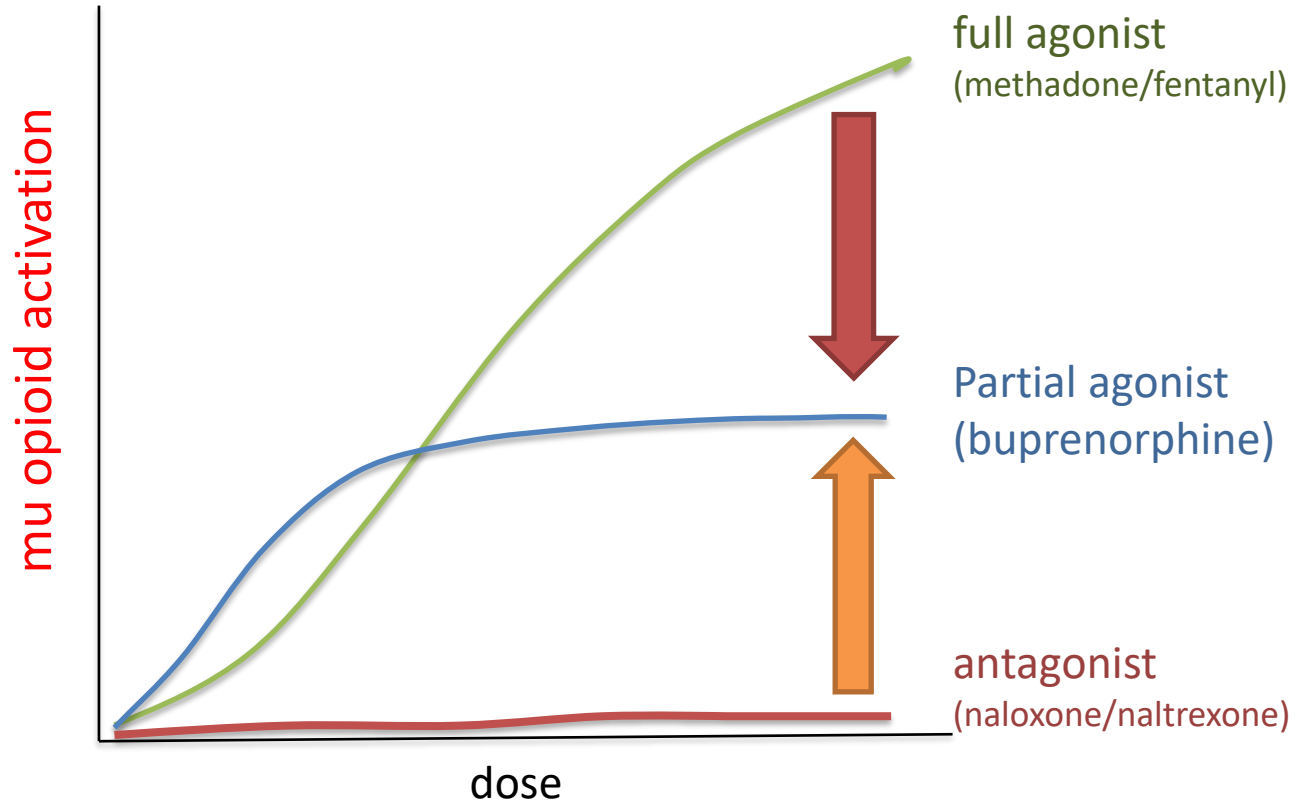
Terminology

- 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 overlapping with ongoing use of heroin/full agonist over 10 or more days; many variations of this protocol are now in use
- 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

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***)

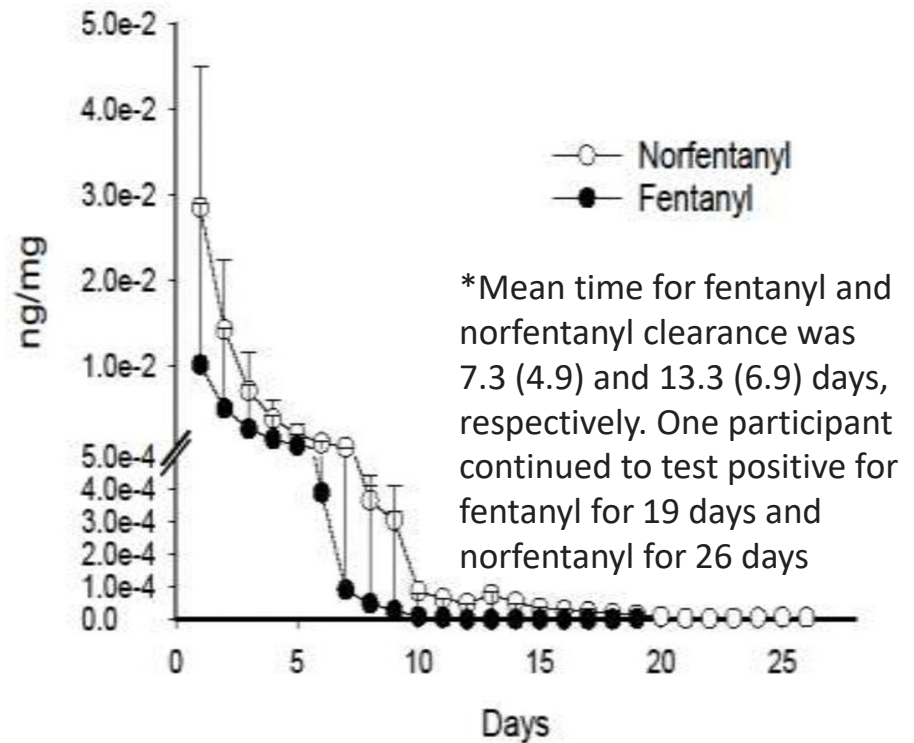
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Fentanyl Pharmacology

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

Fentanyl and Norfentanyl Elimination



*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



Beta-arrestin
Respiratory depression

Comer SD, Cahill CM. Fentanyl: Receptor pharmacology, abuse potential, and implications for treatment. *Neurosci Biobehav Rev.* 2019 Nov;106:49-57. doi: 10.1016/j.neubiorev.2018.12.005. Epub 2018 Dec 5. PMID: 30528374; PMCID: PMC7233332.

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 opioid first
 - a longer interval between last 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

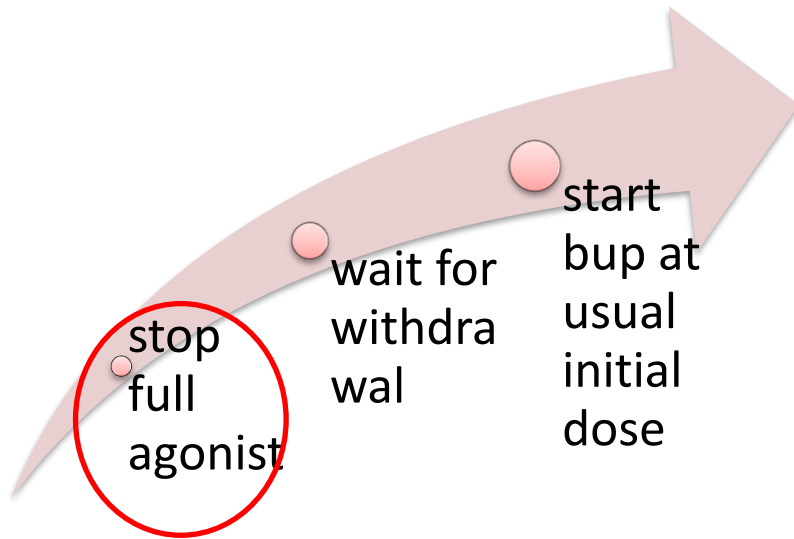
What is Low-dose Buprenorphine Initiation?*

- 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.

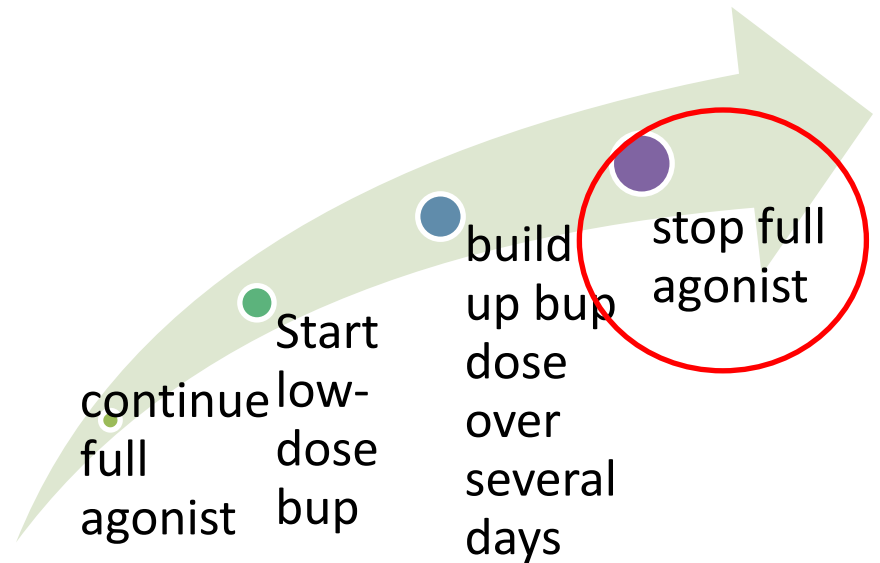
*De Aquino JP, Parida , Sofuoglu M. The Pharmacology of Buprenorphine Microinduction for Opioid Use Disorder. Clin Drug Investig. 2021 May;41(5):425-436. doi: 10.1007/s40261-021-01032-7.

Conventional vs LDBI Approach

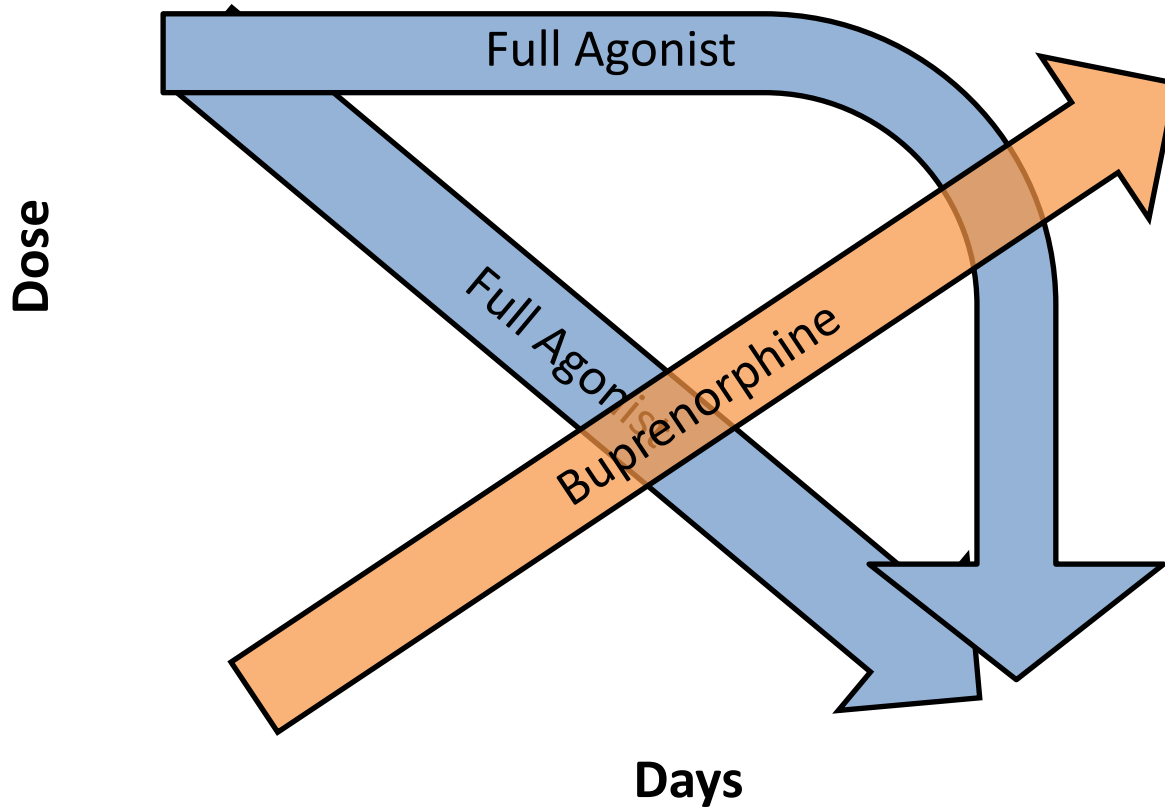
Conventional



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.

Another 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

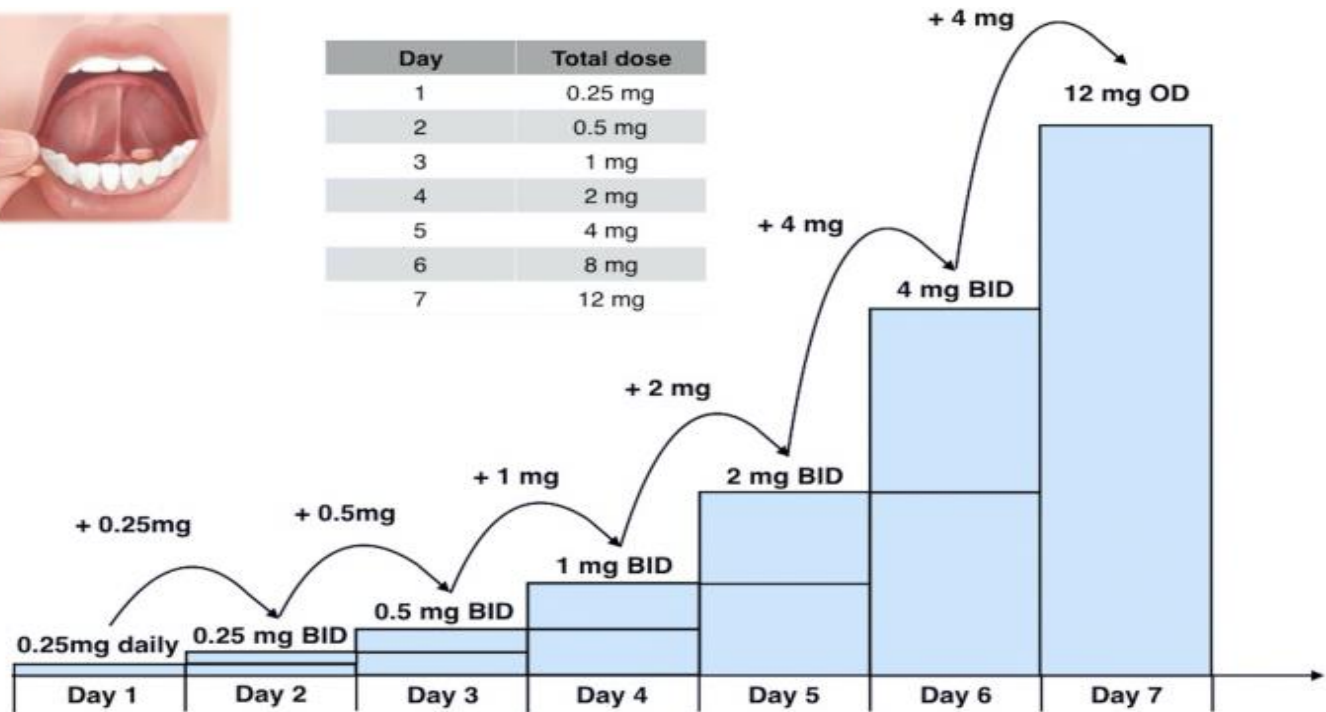
Bup, Buprenorphine; Nlx, naloxone; BID, twice a day; TID, twice a day.

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.

Another Protocol Example*

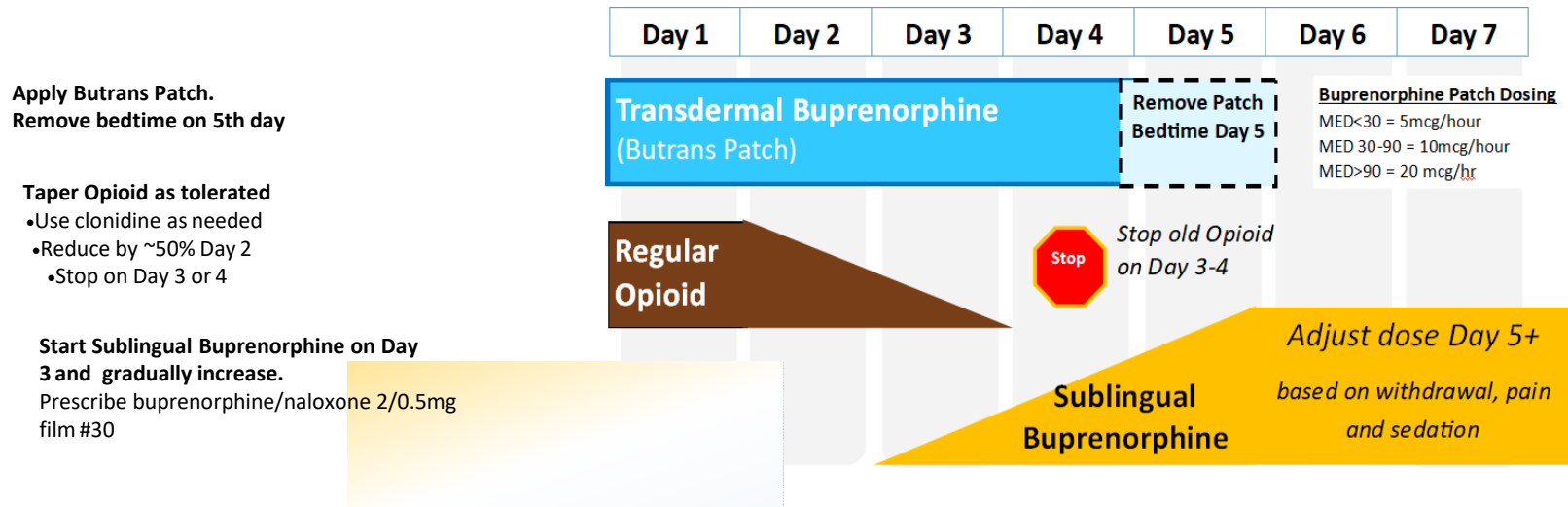


Day	Total dose
1	0.25 mg
2	0.5 mg
3	1 mg
4	2 mg
5	4 mg
6	8 mg
7	12 mg



*Rozylo J, Mitchell K, Nikoo M, Durante SE, Barbic SP, Lin D, Mathias S, Azar P Case report: Successful induction of buprenorphine/naloxone using a microdosing schedule and assertive outreach. *Addict Sci Clin Pract.* 2020 Jan 15;15(1):2. PMID: [31941547](https://pubmed.ncbi.nlm.nih.gov/31941547/)

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



.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/pm/pnz356



U. S. Department of Justice
Drug Enforcement Administration
8701 Morrissette Drive
Springfield, Virginia 22152

www.dea.gov

Aaron Greenblatt, M.D.
Medical Director, University of Maryland Drug Treatment Center
University of Maryland Medical Treatment Center
Addiction Treatment Programs at 1001 West Pratt
1001 West Pratt Street
Baltimore, Maryland 21223
Agreenbl@som.umaryland.edu

G. Malik Burnett, M.D., MBA, MPH
Addiction Medicine Fellow, University of Maryland Medical Center
GMBurnett@som.umaryland.edu

Eric Weintraub, M.D.
Program Sponsor, University of Maryland Drug Treatment Center
Eweintra@som.umaryland.edu

Dear Doctors Greenblatt, Burnett, and Weintraub:

This is in response to your letter dated February 11, 2021, to the Baltimore District Office of the Drug Enforcement Administration (DEA), where you described the University of Maryland Medical Center's (UMMC) difficulties facilitating buprenorphine induction for patients in UMMC's opioid treatment programs for opioid use disorder (OUD). DEA appreciates your correspondence as well as the opportunity to address your inquiry.

In your correspondence, you proposed "the use of transdermal buprenorphine for patients being bridged to definitive buprenorphine maintenance therapy under [21 CFR 1306.07(b)]", and indicated in your correspondence that "[u]nder 21 CFR ... 1306.07(b), a practitioner would be allowed to dispense a transdermal patch to a patient for up to three days at which point the patient would return to clinic in order to initiate maintenance therapy."

In December of 2020, Congress directed DEA to amend that regulation to allow for the dispensation of not more than a three-day supply of narcotic drugs to one person or for one person's use at one time for the purpose of initiating maintenance or detoxification treatment. DEA is in the process of drafting a notice of proposed rulemaking amending 21 CFR 1306.07(b) to comply with this directive. Given your interest in the provision of treatment to those with OUD, you may wish to submit comments to that notice, which will be published in the Federal Register.

"We aren't going to say you can't do it nor are we going to say you can do it. But if you do it...we will be there to make your life a lot harder."

Local Case: "GB"

- 65 M, PMH chronic back pain and hip pain due to OA, lung cancer treated via resection, smoking.
- On methadone, with regular attendance hindered by mobility problems/pain.
- Toxicology positive for methadone, opiates, fentanyl, benzodiazepines, occ cocaine
- Occasionally returns early having taken extra methadone or missing take-home bottles.
- Failed remote monitoring

Local Case: "GB"

- Presents to OTP having missed 1 day of methadone @ 70mg/day (had 1 week of take homes from failed trial of remote monitoring)
- Interested in XR-BUP and an interventional pain specialist referral
- Dispensed a 1 week taper (60,50,40,30,25,20,5) with plan on returning in 1 week to initiate bup. Prescribed clonidine, cyclobenzaprine, loperamide, ondansetron, and trazodone as supportive medications.
- Lost to follow up.

Local Case: "GB"

- 2 weeks later, patient obtains a prescription of oxycodone/APAP 7.5mg/325mg (#24) from PCP office. I encourage him to use this as a bridge off of extramedical opioids.
- Over the first 2 days, takes 10 tablets, plus "3 pills" extramedical opioids because "my stomach had started to cramp up."
- I encouraged him to restrict himself to oxycodone only until remainder were consumed, then microdose bup/nal for induction.
- Followed up by phone and text the following day. Patient expresses appreciation and guarded optimism.
- Over the course of the following month, takes 0.5mg about every other day while continuing to use 1 pill of dope daily, but expresses some willingness to come back in for follow up.

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

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 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 follow a protocol
- Do consider seeking a consultation if you are not sure how to proceed

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

High Dose Buprenorphine Initiation (“Macro dosing”)

- Generating some interest based on a large uncontrolled case series and a few case reports
- Approaches buprenorphine initiation differently than LDBI
- Unclear if this would work well in the presence of fentanyl /methadone
- Rationale for its application in the large ED-based case series was patient’s inability to fill discharge prescription in a timely manner, not to mitigate the risk of precipitated withdrawal



Original Investigation | Substance Use and Addiction

High-Dose Buprenorphine Induction in the Emergency Department for Treatment of Opioid Use Disorder

Andrew A. Herring, MD; Aidan A. Vosooghi, MS; Joshua Luftig, PA; Erik S. Anderson, MD; Xiwen Zhao, MS; James Dziura, PhD; Kathryn F. Hawk, MD, MHS; Ryan P. McCormack, MD, MS; Andrew Saxon, MD; Gail D'Onofrio, MD, MS

Abstract

IMPORTANCE Emergency departments (EDs) sporadically use a high-dose buprenorphine induction strategy for the treatment of opioid use disorder (OUD) in response to the increasing

CONCLUSIONS AND RELEVANCE These findings suggest that high-dose buprenorphine induction, adopted by multiple clinicians in a single-site urban ED, was safe and well tolerated in patients with untreated OUD. Further prospective investigations conducted in multiple sites would enhance these findings.

Key Points

Question Is high-dose (>12 mg) buprenorphine induction safe and well

Key Points

Question Is high-dose (>12 mg) buprenorphine induction safe and well tolerated in patients with untreated opioid use disorder who present to the emergency department?

Findings In this case series of 579 cases, 54 clinicians followed a high-dose buprenorphine (monoproduct) protocol. There were no documented episodes of respiratory depression or excessive sedation, and precipitated withdrawal was rare (0.8% of cases) and was not associated with dosing.

Meaning These findings suggest that high-dose buprenorphine induction, adopted by multiple clinicians in a single-site, urban emergency department, was safe and well tolerated in patients with untreated opioid use disorder.

Limitations

- Retrospective chart review
- Single ED-based
- No control group
- Many exclusions
- No information about which opioids the patients were using
- No drug testing data included, but their test panel does not appear to have included fentanyl
- Extent of fentanyl prevalence in the area not available

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