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Clinical strategies for low-dose overlap initiation of buprenorphine and potential barriers to use

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Background

Buprenorphine low-dose overlap initiation (LDOI) is a strategy using a very low dose of buprenorphine (0.2 to 0.5 mg), sometimes called a microdose, while the full agonist opioid is continued. The goal of LDOI is to remove the need for abstinence from opioids prior to initiation of buprenorphine while reducing the risk of precipitated withdrawal.[1] LDOI is optimal for patients with concerns for precipitated withdrawal as it allows for self-tapering and/or continuing full agonist opioids temporarily while transitioning to buprenorphine. Buprenorphine is slowly increased to displace the original full agonist opioid as the full agonist opioid is tapered off. Buprenorphine titration is continued to the lowest effective dose based on withdrawal and cravings. LDOI can be utilized in complex cases in which a patient is at a greater risk of withdrawal, such as when transitioning from highly lipophilic, long-acting, or high-dose opioids (eg, methadone or fentanyl). There is no standardized or preferred method for LDOI as robust clinical trial data does not exist at this time. Multiple strategies for LDOI have been introduced with the first being the Bernese method in 2010.[2] A summary of common LDOI methods are listed in Table 1. LDOI should be tailored to the patient and setting with consideration of appropriate dose, dosing interval, and product.

Illustrative Case

A 28-year-old male presents to the emergency room requesting assistance with fentanyl cessation. He has been using up to 50 nonpharmaceutical fentanyl pills per day for the last 8 months with intolerable withdrawal within a few hours of attempting to stop. He attempted to use cocaine to manage withdrawal symptoms, leading to dehydration and rhabdomyolysis with blood urea nitrogen of 42 mg/dL, creatinine of 1.8 mg/dL, and creatine kinase of 2000 mg/dL. A urine drug screen detected fentanyl and cocaine metabolite, whereas other testing was unremarkable. He last swallowed fentanyl in the parking lot immediately before arrival. He is not currently experiencing withdrawal symptoms due to proximity of use. A rapid, low-dose buprenorphine induction strategy is chosen to quickly initiate treatment and minimize withdrawal. An essential LDOI was completed. Due to the timing of fentanyl administration, a high percentage of opioid receptors were expected to have been occupied at the time of buprenorphine initiation, and further full agonist opioid dosing was not required in this case. The initial strategy is to begin a fourth of a 2 mg buprenorphine tablet (0.5 mg) sublingually every 3 hours with plans to escalate doses over a 24-hour period. Pharmacy and nursing both express concerns about splitting buprenorphine tablets, and nursing policy prohibits quartering of medications. Intravenous buprenorphine is not available.

Discussion

In practice, barriers often arise to LDOI product selection due to product availability, formulation restrictions, and insurance concerns.[3,4] Whereas insurance coverage of buprenorphine products is expanding, some patients are still

Practice Points

- LDOI is a useful induction option for patients transitioning from full agonist opioids to buprenorphine.
- LDOI minimizes the risk of precipitated withdrawal and eliminates the need for complete opioid abstinence.
- There is no standardized method of LDOI. Dosing strategies may vary based on available products, hospital formularies, and patient-specific factors, such as care setting and insurance.
- Hospitals may face obstacles, such as insurance limitations, formulary restrictions, or policies against splitting tablets or films.

impacted by limited insurance coverage.[5] For this reason, more costly formulations (ie, Brixadi and Sublocade) may not be feasible options for initiation in the acute care setting. The basic structure of gradual transition from full agonist to partial agonist remains the same; however, health care systems should choose specific strategies based on their formulary and patient populations. All available products that may be used for LDOI are outlined in Table 2.

Current use of low-dose initiation strategies are considered off-label and may require splitting buprenorphine tablets or films in half or quarters to obtain the low dosages required, which may be prohibited by some hospitals due to safety concerns or lack of explicit recommendation by the FDA.[6] Splitting may also be difficult for certain patients, such as elderly patients, who are manipulating products in the outpatient setting. Tablet products may prove more difficult to split than film formulations, and this has less stability data available.[7] There are various methods that can be used to split films with varying uniformity and stability.[8] DeWeese et al describe barriers that providers at a hospital faced with splitting of buprenorphine

TABLE 1: Buprenorphine low dose overlap initiation strategies

Method	Product(s)	Considerations	Day	BUP Schedule
Azar method[11]	Fentanyl patch then Suboxone	Fentanyl patches are used to bridge from long-acting opioid to buprenorphine; 25 mcg/h fentanyl patch q3 days applied for days 1-6, then patch is discontinued; Suboxone splitting not required	1-6	None
Bernese method[2]	Suboxone	Overlap with full agonist for 5 days; requires substantial Suboxone splitting (as low as 1/10 tablet or film)	1	1 mg q1-2 hours × 2 doses, then 2 mg q2 hours × 3 doses
			2	8 mg/2 mg
			3	0.8 mg + 0.2 mg
			4	2 mg + 2.5 mg
			5	2.5 mg BID
			6	2.5 mg + 4 mg
			7	4 mg BID
			8	4 mg BID
			9	8 mg + 4 mg
7-day sublingual cross taper[12]	Suboxone	Full agonist slowly self-tapered with goal to discontinue by day 7; requires Suboxone splitting (as low as 1/4 tablet or film)	1	0.5 mg daily
			2	0.5 mg BID
			3	1 mg BID
			4	2 mg BID
			5	3 mg BID
			6	4 mg BID
			7	6 mg BID
Rapid overlap initiation[9]	Suboxone	Overlap with full agonist for 1-3 days; strict schedule may require dosing overnight; requires Suboxone splitting (as low as 1/4 tablet or film)	1	0.5 mg q6 hours
			2	1 mg q6 hours
			3	2 mg q6 hours
			4	≥ 12 mg daily
Buprenorphine transdermal patch method[13]	Butrans patch then Suboxone	Overlap with full agonist for 3 or more days; some regimens advise stopping full opioid agonists when patches are removed; Suboxone splitting not required	1	Start 20 mcg patch
			2	Add 2nd 20 mcg patch (total 40 mcg)
			3	Add 3rd 20 mcg patch (total 60 mcg)
			4	Continue patches ± sublingual (2 mg BID)
			5	Continue patches ± sublingual (4 mg BID)
			6	Remove patches + sublingual (8 mg BID)
			7	≥ 16 mg daily (range 8-32 mg)[a]

BID = twice daily; BUP = buprenorphine; IP = inpatient; OP = outpatient; q = every; TID = three times daily.
[a]BUP dose will depend on if sublingual buprenorphine was given with the patches (eg, higher end of range if patch + sublingual).

TABLE 2: Available buprenorphine products[15-20]

Brand Name	Dosage Form	Generic Available	FDA-Approved Indication	Available Strengths
Buprenorphine monotherapy products				
Belbuca	Buccal film	No	Pain	75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, 900 mcg
Brixadi[a]	Solution, extended release injection (subcutaneous)	No	OUD	Weekly: 8 mg/0.16 mL, 16 mg/0.32 mL, 24 mg/0.48 mL, 32 mg/0.64 mL Monthly: 64 mg/0.18 mL, 96 mg/0.27 mL, 128 mg/0.36 mL
Buprenex[b]	Injection (intravenous or intramuscular)	Yes	Pain	0.3 mg/mL
Butrans	Transdermal patch system	Yes	Pain	5 mcg/h, 7.5 mcg/h, 10 mcg/h, 15 mcg/h, 20 mcg/h
Sublocade[a]	Solution, extended release injection (subcutaneous)	No	OUD	100 mg/0.5 mL, 300 mg/1.5 mL
Subutex[b]	Sublingual tablet	Yes	OUD	2 mg, 8 mg
Buprenorphine and naloxone combination products				
Suboxone	Sublingual film	Yes	OUD	2 mg/0.5 mg, 4 mg/1 mg, 8 mg/2 mg, 12 mg/3 mg
Suboxone[b]	Sublingual tablet	Yes	OUD	2 mg/0.5 mg, 8 mg/2 mg
Zubsolv	Sublingual tablet	No	OUD	0.7 mg/0.18 mg, 1.4 mg/0.36 mg, 2.9 mg/0.71 mg, 5.7 mg/1.4 mg, 8.6 mg/2.1 mg, 11.4 mg/2.9 mg

OUD = opioid use disorder.
[a]REMS program requirements.
[b]Brand name product no longer available in the United States.

products due to a local hospital protocol and outlines steps taken to overcome these barriers. This included creation of a halving and quartering policy for LDOI, transitioning splitting responsibilities from floor nursing staff to pharmacy to allow for presplit doses, and increased education to both nursing and pharmacy staff members with involvement in the LDOI process.[9] The Howard Street method also outlines a LDOI protocol that used blister-pack dosing, which allowed for similar retention rates and overall well-managed withdrawal for the majority of patients.[10] This method, however, was used in a community-based setting rather than an inpatient hospital unit. See Table 3 for dose conversions between various products that may be useful when initiating buprenorphine. When available, stability data should be used as supporting evidence if pursuing a change in hospital policy to allow for splitting of buprenorphine tablets or films.

The patient case above outlines a complex case of opioid withdrawal due to high-dose, synthetic opioid use with acute medical comorbidities. Concerns by those administering the medication and hospital policy created a barrier for LDOI in this case.

The following steps should be considered when treating clinicians face similar barriers in practice:

1. Become familiar with which buprenorphine products are on formulary and consider advocating for the addition of buprenorphine products to use for LDOI.
2. Educate interprofessional staff (eg, providers, nursing, pharmacy) and the patient regarding off-label use of buprenorphine for LDOI.
3. Use the Clinical Opiate Withdrawal Scale throughout LDOI to evaluate the severity of any withdrawal symptoms.
4. Use as-needed medications (eg, hydroxyzine for anxiety and loperamide for diarrhea) during the LDOI process.
5. Titrate buprenorphine during admission to reach a goal dose of 16 mg, if possible, prior to discharge.

TABLE 3: Approximate dose conversion between buprenorphine products[a,b,14,21,22]

BUP SL Tablet	BUP/NLX SL Tablet/Film	Zubsolv SL Tablet	Belbuca Buccal Film	BUP TD Patch
0.5 mg	0.5 mg/0.125 mg		225 mcg	20 mcg/h
1 mg	1 mg/0.25 mg		450 mcg	
2 mg	2 mg/0.5 mg	1.4 mg/0.36 mg	900 mcg	
4 mg	4 mg/1 mg	2.9 mg/0.71 mg		
8 mg	8 mg/2 mg	5.7 mg/1.4 mg		
12 mg	12 mg/3 mg	8.6 mg/2.1 mg		
16 mg	16 mg/4 mg	11.4 mg/2.9 mg		
24 mg	24 mg/6 mg	17.2 mg/4.1 mg		

BUP = buprenorphine; BUP/NLX = buprenorphine/naloxone; SL = sublingual; TD = transdermal.
[a]Bioavailability (F) varies between products and must be taken into consideration when switching between formulations.
[b]All dose conversions are approximate based on dose equivalency and maximum concentration calculations.

Conclusion

LDOI allowed for a safe and comfortable transition to buprenorphine during admission. Although this is not a traditional LDOI scenario, the same principles apply due to the timing of fentanyl administration and the need for opioid receptor occupancy to slowly be replaced with low-dose buprenorphine. Awareness of formulary alternatives, flexibility in proposed strategy, and knowledge of appropriate conversions allowed for this patient to be treated appropriately despite facing initial barriers.

References

1. Spreen LA, Dittman EN, Quirk KC, Smith MA. Buprenorphine initiation strategies for opioid use disorder and pain management: a systematic review. Pharmacotherapy. 2022;42(5):411-27. DOI: 10.1002/phar.2676
2. Hämmig R, Kemter A, Strasser J, Bardeleben U, Gugger B, Walter M, et al. Use of microdoses for induction of buprenorphine treatment with overlapping full opioid agonist use: the Bernese method. Subst Abuse Rehabil. 2016;7:99-105. DOI: 10.2147/SAR.S109919
3. Nguyen TD, Chua KP, Andraka-Christou B, Bradford WD, Simon K. Trends in buprenorphine coverage and prior authorization requirements in US commercial formularies, 2017-2021. JAMA Health Forum. 2022;3(7):e221821. DOI: 10.1001/jamahealthforum.2022.1821
4. Mark TL, Parish WJ, Zarkin GA. Association of formulary prior authorization policies with buprenorphine-naloxone prescriptions and hospital and emergency department use among Medicare beneficiaries. JAMA Netw Open. 2020;3(4):e203132. DOI: 10.1001/jamanetworkopen.2020.3132
5. Olfson M, Zhang VS, King M, Mojtbai R. Changes in buprenorphine treatment after medicaid expansion. Psychiatr Serv. 2021;72(6):633-40. DOI: 10.1176/appi.ps.202000491
6. Weimer MB, Guerra M, Morrow G, Adams K. Hospital-based buprenorphine micro-dose initiation. J of Addict Med. 2021;15(3):255-71. DOI: 10.1097/ADM.0000000000000745
7. Elliott I, Mayxay M, Yeuichaixong S, Lee SJ, Newton PN. The practice and clinical implications of tablet splitting in international health. Trop Med Int Health. 2014;19(7):754-60. DOI: 10.1111/tmi.12309
8. Reindel KL, DeAngelis MJ, Ferrara AS, Conn KM, Phillips EM, Corigliano AT, Zhao F. An exploratory study of suboxone (buprenorphine/naloxone) film splitting: cutting methods, content uniformity, and stability. Int J Pharm Compd. 2019;23(3):258-63. PMID: 31085795
9. DeWeese JP, Krenz JR, Wakeman SE, Peckham AM. Rapid buprenorphine microdosing for opioid use disorder in a hospitalized patient receiving very high doses of full agonist opioids for acute pain management: titration, implementation barriers, and strategies to overcome. Subst Use Addctn J. 2021;42(4):506-11. DOI: 10.1080/08897077.2021.1915914
10. Noel M, Abbs E, Suen L, Samuel L, Dobbins S, Geier M, et al. The Howard Street method: a community pharmacy-led low dose overlap buprenorphine initiation protocol for individuals using fentanyl. J Addict Med. 2023;17(4):e225-61. DOI: 10.1097/ADM.0000000000001154
11. Azar P, Nikoo M, Miles I. Methadone to buprenorphine/naloxone induction without withdrawal utilizing transdermal fentanyl bridge in an inpatient setting—Azar method. Am J Addict. 2018;27(8):601-4. DOI: 10.1111/ajad.12809
12. CA Bridge Protocol. Acute pain management in patients on buprenorphine (bup) treatment for opioid use disorder. California Bridge Program. 2021. Available from: https://bridgetotreatment.org/addiction-treatment/ca-bridge/
13. Suen LW, Lee TG, Silva M, Walton P, Coffin PO, Geier M, et al. Rapid overlap initiation protocol using low dose buprenorphine for opioid use disorder treatment in an outpatient setting: a case series. J Addict Med. 2022. DOI: 10.1097/ADM.0000000000000961
14. Ghosh SM, Klaire S, Tanguay R, Manek M, Pouya A. A review of novel methods to support the transition from methadone and other full agonists buprenorphine/naloxone sublingual in both community and acute care settings. Canadian J Addiction. 2019;10(4):41-50. DOI: 10.1097/CXA.0000000000000072
15. BioDelivery Sciences International, Inc. BELBUCA (buprenorphine) buccal film, soluble. 2021 [rev 2023 Dec; cited 2024 Sept]. In DailyMed [Internet]. [1981]. National Library of Medicine (US). Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=bc2b7a3d-72cf-497c-95b0-ba2b71f63c64
16. Braeburn, Inc. BRIXADI (buprenorphine injection). 2023. [rev 2023 Dec; cited 2024 Sept]. In: DailyMed [Internet]. National Library of Medicine (US). [2021]. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=5d8a8fd0-8619-422a-a664-d1d2e8970f48
17. Purdue Pharma L. P. BUTRANS (buprenorphine patch, extended release). [rev 2023 Dec; cited 2024 Sept]. In: DailyMed [Internet].] [1981]. National Library of Medicine (US). [2021]. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=794aa355-66de-41b8-aedf-f2c40f6bc664
18. Indivior Inc. SUBLOCADE (buprenorphine solution). 2023. [rev 2023 Dec; cited 2024 Sept]. In: DailyMed [Internet]. National Library of Medicine (US). [2021]. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=6189fb21-9432-45f8-8481-0bfaf3ccde95
19. Indivior Inc. SUBOXONE (buprenorphine hydrochloride, naloxone hydrochloride) film, soluble. [rev 2023 Dec; cited 2024 Sept]. In: DailyMed [Internet]. National Library of Medicine (US). [2002]. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8a5edcf9-828c-4f97-b671-268ab13a8ecd
20. Orexo US, Inc. ZUBSOLV (buprenorphine hydrochloride, naloxone hydrochloride) tablet, orally disintegrating. [rev 2023 Dec; cited 2024 Sept]. In: DailyMed [Internet]. National Library of Medicine (US). [2002]. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=5f5cfcfe-d52b-49e6-8fe4-550477332dd2
21. Weimer MB, Guerra M, Morrow G, Adams K. Hospital-based buprenorphine micro-dose initiation. J Addict Med. 2021; 15(3):255-7. DOI: 10.1097/ADM.0000000000000745
22. Orexo US, Inc. ZUBSOLV (buprenorphine and naloxone) sublingual tablets. Dose conversion calculator. Available from: https://www.zubsolv.com/healthcareprofessionals/about-zubsolv/dose-conversion-calculator/