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Low-Dose Buprenorphine Initiation in Hospitalized Adults with Opioid Use Disorder: A Retrospective Cohort Analysis

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Abstract

Objectives: Patients with opioid use disorder (OUD) can initiate buprenorphine without requiring a withdrawal period through a low-dose (sometimes referred to as “micro-induction”) approach. While there is growing interest in low-dose buprenorphine initiation, current evidence is limited to case reports and small case series.

Methods: We performed a retrospective cohort study of patients with OUD seen by a hospital-based addiction medicine consult service who underwent low-dose buprenorphine initiation starting during hospital admission. We then integrated our practice-based experiences with results from the existing literature to create practice considerations.

Results: Sixty-eight individuals underwent 72 low-dose buprenorphine initiations between July 2019 and July 2020. Reasons for low-dose versus standard buprenorphine initiation included co-occurring pain (91.7%), patient anxiety around the possibility of withdrawal (69.4%), history of precipitated withdrawal (9.7%), opioid withdrawal intolerance (6.9%), and other reason/not specified (18.1%). Of the 72 low-dose buprenorphine initiations 50 (69.4%) were completed in the hospital, 9 (12.5%) transitioned to complete as an outpatient, and 13 (18.1%) were terminated early. We apply our experiences and findings from literature to recommendations for varied clinical scenarios, including acute illness, co-occurring pain, opioid withdrawal intolerance, transition from high dose methadone to buprenorphine, history of precipitated withdrawal, and rapid hospital discharge. We share a standard low-dose initiation protocol with potential modifications based on above scenarios.

Conclusions: Low-dose buprenorphine initiation offers a well-tolerated and versatile approach for hospitalized patients with OUD. We share lessons from our experiences and the literature, and provide practical considerations for providers.

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Keywords

hospital; buprenorphine; microdose; induction; opioid-related disorders

Introduction

Between 2005 and 2017, the rate of hospitalizations and emergency department visits in the United States due to complications related to opioid use disorder (OUD) more than doubled.[1] Increasingly, hospital and outpatient clinicians are prescribing and managing medications for opioid use disorder (MOUD), including buprenorphine.[2] Starting buprenorphine during hospital admission is associated with decreased overdose risk and increased post-hospital treatment engagement.[3,4] Traditional or standard buprenorphine initiation require patients to completely stop opioids and be in moderate withdrawal prior to taking the first dose.[5] Administering buprenorphine too soon or with too high a first dose can lead to precipitated withdrawal due to buprenorphine's high affinity for the μ-opioid receptor with concurrent low receptor activation.[6] This may be especially true for patients using fentanyl or other high potency synthetic opioid analogs,[7] which are increasingly prevalent contaminants in the North American drug supply.[8] The standard approach to starting buprenorphine in the hospital can be challenging due to patients' severe illness, chronic pain, and anxiety around withdrawal.[9–12,13] There is therefore an urgent need for strategies to reduce barriers to in-hospital buprenorphine initiation to increase accessibility to this lifesaving medication.

An alternative to traditional initiation is low-dose buprenorphine initiation. First described by Hämmig et al, low-dose buprenorphine initiation (sometimes referred to as "micro-induction") using the Bernese method reduces the severity or avoids the need for withdrawal before initiation.[14] However, the evidence for this promising method is limited to case reports and small case series totaling 63 patient experiences in 20 publications.[12,13] Reports describe low-dose buprenorphine initiation in ambulatory and hospital settings. They provide a variety of approaches, including rapid opioid taper with cross-titration of buprenorphine,[12,13,15–17] up-titration of buprenorphine and opioids followed by opioid taper,[12,13,18] buprenorphine up-titration with stable adjuvant opioid dose, and as a transition to extended-release buprenorphine.[9,10,12,13,19,20] Existing literature describes low-dose buprenorphine initiation from various full agonist opioids, including methadone,[9,12,13,21] injectable opioid agonist therapy,[9,12,13,18] and illicitly manufactured fentanyl[9,12,13,16] or insufflated heroin.[14] Reports present various clinical scenarios, including patients who have failed attempts at traditional initiation due to intolerable withdrawal symptoms,[12,13,14,16] transition from high dose methadone,[9,10,12,13,21] and complicated chronic pain.[12,13,18,22]

Missing from the literature is a summary of practical considerations for hospital-based low-dose buprenorphine initiation that considers various clinical scenarios including: 1) management of co-occurring acute or chronic pain 2) patients with severe co-occurring medical illness 3) peri-operative management and 4) rapid hospital discharge and transition to outpatient follow-up. Thus, we reviewed the existing literature on low-dose buprenorphine initiation and synthesized these findings with a comprehensive retrospective analysis of

low-dose initiation and our own practice experience over the course of a year to provide practical considerations for hospital-based, low-dose buprenorphine initiation.

Methods

Setting and study design

We performed a retrospective cohort study of patients with OUD who underwent low-dose buprenorphine initiation at an urban, academic medical center between July 2019 and July 2020. The OHSU institutional review board approved all study procedures.

All patients were seen by the Improving Addiction Care Team (IMPACT), an addiction medicine consult service that includes an interprofessional team of addiction trained clinicians (addiction medicine physicians, a nurse practitioner, and physician assistant), social workers, and peers with lived experience in recovery. IMPACT sees patients hospitalized for general medical or surgical indications and provides substance use disorder (SUD) assessments and treatment, including initiating medications for opioid use disorder. Most IMPACT patients are medically and socially complex and are not seeking addiction treatment at the time of hospital admission. IMPACT sees patients with any SUD diagnosis, including opioids, stimulants, alcohol, and other substances (excluding tobacco use disorder alone). Previous research describes IMPACT's design and evaluation.[4,23–30]

Data collection and analysis

We prospectively tracked IMPACT patients with opioid use disorder or opioid dependence (diagnosed by DSM-V criteria) who underwent or attempted a low-dose buprenorphine initiation using an electronic registry.[31] Subsequently, we abstracted electronic health record data from all these patients. If patients had more than one attempt at a low-dose initiation, we included each unique attempt. We selected variables based on current literature and research team discussions. Variables included: Age, gender, race, ethnicity, insurance type, housing status, admission diagnosis, SUD diagnoses, mental health diagnoses, days admitted to hospital, prior buprenorphine prescription, methadone use during current admission, opioid medications prescribed in the hospital during the 24 hours prior to low-dose initiation, the primary reason for low-dose initiation, number of days needed to complete low-dose initiation, outcome of low-dose initiation, any reasons for not completing the low-dose initiation, reported symptoms, and if the patient left the hospital prematurely. All in-hospital opioid medications prescribed in the hospital 24 hours prior to low-dose initiation were converted to morphine milligram equivalents (MME) and summed for each low-dose buprenorphine initiation.[32] A completed low-dose initiation was defined as reaching 16 mg buprenorphine/day, or reaching a lower, stable buprenorphine dose through shared-decision making. We analyzed data using descriptive statistics in RStudio version 3.6.1.[33]

Finally, we integrated findings from the existing literature with our clinical addiction medicine experience to summarize practice considerations according to the most common clinical scenarios encountered in the hospital care setting.

Results

Sixty-eight patients underwent 72 low-dose buprenorphine initiations (table 1). Patients were primarily male (60.3%), white (95.6%), not Hispanic or Latino (94.1%), in stable housing (64.7%), and insured (100%). Average age was 45 years (range 19–73). Patients had diagnoses of OUD (92.6%), methamphetamine use disorder (52.9%), alcohol use disorder (13.2%), sedative/hypnotic use disorder (10.3%), and cocaine use disorder (7.4%). One patient (4.6%) was diagnosed with opioid dependence and chronic pain but did not have any SUD diagnoses. Many patients (52.9%) had co-occurring mental health diagnoses (anxiety, depression, obsessive-compulsive disorder, post-traumatic stress disorder), and 57.4% had previously trialed buprenorphine. Patients had mean hospital length of stay of 24 days (range 3–79 days).

The mean prescribed MME 24 hours prior to low-dose initiation was 198 (standard deviation [SD] 98). We could not determine MMEs for six patients (8.8%) who started low-dose initiation within 24 hours of hospital admission (and whose outpatient opioid intake was not quantifiable).

Reasons for low-dose initiation (table 2), versus standard initiation, included co-occurring pain (91.7%), patient anxiety around the possibility of withdrawal (69.4%), a history of precipitated withdrawal (9.7%), opioid withdrawal intolerance (6.9%), and other or unspecified reason (18.1%). The mean duration of in-hospital low-dose buprenorphine initiation was six days (SD 2.7), and ranged from 1 to 15 days. Fifty patients (69.4%) completed low-dose initiation in the hospital by reaching a dose of 16 mg of buprenorphine per day or by reaching a different, stable dose through shared-decision making. Among patients completing low-dose initiation in the hospital, the mean days of low-dose initiation was 7.6 (SD 1.9) and ranged from 3 to 15 days. Nine patients (12.5%) began low-dose initiation in the hospital and were scheduled to complete it as an outpatient. One patient completed low-dose initiation, asked to discontinue buprenorphine, and then opted to begin buprenorphine by low-dose initiation again prior to discharge with a plan to complete as an outpatient. There were 13 (18.1%) low-dose initiations that were discontinued. Reasons for discontinuation varied. One patient attributed lower extremity weakness to the buprenorphine and asked to stop the low-dose initiation. Another patient stopped low-dose initiation after they were transitioned to comfort care measures due to terminal illness. Other patients noted wanting to return home (1 of 13, 7.8%), fear of inadequate pain control (5 of 13, 38.4%), and requesting to be switched to methadone (2 of 13, 15.4%). We were unable to determine reason for stopping low-dose initiation for three patients (23%), of which two left the hospital prematurely during the low-dose initiation. For one patient, low-dose initiation was stopped twice before successfully completing the third low-dose initiation. Another patient ended a low-dose initiation during one hospitalization, but then completed low-dose initiation without complication during a separate admission. Ultimately, 50 (73.5%) patients completed low-dose buprenorphine initiation.

We were unable to determine if symptoms reported during the low-dose initiation resulted from buprenorphine administration or from ongoing illnesses. Chart notes from 22 (30.6%) low-dose initiations reported symptoms during the low-dose initiation period. These

included anxiety, agitation, drowsiness, diaphoresis, headache, hot and cold flashes, nausea, muscle fatigue, pain, and vomiting.

Practice Considerations

We synthesized the current literature and our experiences into six primary practice considerations for in-hospital low-dose buprenorphine initiation (table 3).

Acute, severe illness

Many patients are interested in starting buprenorphine treatment, but discontinuing current opioids and experiencing withdrawal for a buprenorphine initiation would be intolerable during their acute and severe medical illness or injury. Further, acute illness such as fever from infection can mimic opioid withdrawal symptoms, making it difficult to assess opioid withdrawal severity in this category of hospitalized patients. Low-dose buprenorphine initiation avoids the need for withdrawal before beginning buprenorphine. We share a 7-day, standard low-dose initiation protocol (table 4) for patients with acute illness. Patients with respiratory disease[18] or taking sedatives such as benzodiazepines[34] may require more frequent monitoring due to opioid-related respiratory depression. However, low-dose initiation remains a safe option for these patients in the highly monitoring hospital setting.

Co-occurring pain

In our experience, co-occurring pain (whether acute or chronic) was the most common reason cited for choosing low-dose initiation over traditional induction. Many patients wanted buprenorphine treatment and not methadone yet had acute pain, limiting acceptability and feasibility of traditional initiation. Some patients cited personal preference for wanting buprenorphine instead of methadone. Others had limited post-hospitalization methadone access because of either need for skilled nursing facility or rural geography. Having a clear plan for managing co-occurring pain can support successful low-dose initiation. We did not find that low-dose initiation resulted in increased pain experience. Strategies may include administering supplemental high-affinity opioids for patients who experience breakthrough pain, and administering buprenorphine three to four times daily as analgesic effects of buprenorphine are more short-acting than effects on craving.[35] These principles apply regardless of pain due to surgical or non-surgical sources. We use shared-decision making to determine whether to taper or stop additional opioids after the low-dose buprenorphine initiation is complete.[15–17]

History of precipitated withdrawal

Among patients who have experienced or witnessed precipitated withdrawal, the thought of re-experiencing this can induce a post-traumatic syndrome similar to withdrawal itself with palpitations, anxiety, diaphoresis, and nausea. A low-dose initiation approach is an attractive and compassionate option for these patients. We recommend addressing patients' anxiety by taking extra time to explain the physiology behind low-dose buprenorphine initiation, and collaborating with the patient and medical care team to offer adjunctive medications for managing anxiety, including medications such as hydroxyzine or tizanidine (while avoiding benzodiazepines).[36]

Opioid withdrawal intolerance

Many patients present to the hospital in the initial stages or ongoing development of opioid withdrawal. ASAM Guidelines recommend a clinical opioid withdrawal score (COWS) of 11 or more before initiating traditional buprenorphine initiation,[9] but some patients cannot tolerate mild or moderate withdrawal and may risk leaving the hospital prematurely.[37] In these instances, we recommend treating acute withdrawal with up to 40 mg of methadone per day and simultaneously beginning a low-dose initiation using a buprenorphine patch. Though low-dose buprenorphine initiation seeks to minimize withdrawal symptoms, there may be periods between doses, during up-titration of buprenorphine, or down-titration of other opioids where withdrawal symptoms develop. Some strategies to manage and minimize withdrawal symptoms include optimized dosing schedules (increase dosing frequency to 3 to 4 times daily), slowly down-titrating adjuvant opioids, and discussing readiness to increase buprenorphine dose. After low-dose buprenorphine initiation is complete, methadone or other adjuvant opioids can be more rapidly down-titrated or stopped.

Transition from high dose methadone

Many patients with acute and chronic illness face insurmountable barriers to accessing methadone maintenance treatment after discharging from the hospital, particularly those needing care at a rehabilitation center or skilled nursing facility setting.[38,39] Patients previously on methadone maintenance may want or need to switch from methadone to buprenorphine during hospitalization. In these instances, where possible, we have utilized a longer low-dose initiation, tapering methadone to approximately 80 mg over the first few days, and then continuing methadone at that dose while slowly up-titrating buprenorphine via low-dose initiation. Our experience supports ability to successfully discontinue methadone by around day 10, while up-titrating buprenorphine to an appropriate dose. Similar approaches to transitioning from methadone to buprenorphine have also been described.[9,10,21]

Rapid hospital discharge

Hospital discharge readiness can be unpredictable. Patients may not be amenable to buprenorphine treatment until just before discharge or they may be ready for discharge earlier than anticipated. In these situations, rapid low-dose initiation over three days is an option.[15] However, our experience suggests that many hospitalized patients are comfortable with a longer low-dose initiation to be completed after hospital discharge. For these patients, we arrange close outpatient follow up and use teach-back to ensure they understand the initiation schedule. We contact outpatient clinicians to answer questions and foster understanding of the low-dose buprenorphine initiation protocol, and include family and caregivers in patient education efforts.

Discussion

Our retrospective cohort study builds on existing single case reports or small case series, sharing our experiences from 72 in-hospital low-dose buprenorphine initiations. This more than doubles existing published cases from 63 patients across 20 publications[12,13] to 131

patients and 135 low-dose initiation experiences. We found that low-dose initiation can address significant barriers associated with the traditional buprenorphine initiation and can expand feasibility and acceptability of buprenorphine for hospitalized patients. Our experience supports that low-dose buprenorphine initiation can reduce the suffering often associated with standard initiation by eliminating the need for withdrawal and allowing concomitant full-agonist opioids. It also lends itself to easily-implemented protocols that can be customized based on patient needs and preferences.

There are several limitations to this study. Our study population was racially and ethnically homogenous. Future studies should examine low-dose initiation in a diversity of patient populations. We did not assess patient experiences with low-dose initiation directly and this is an area for future research. Patients were not followed after hospital discharge so we were unable to determine if patients completed low-dose initiation as an outpatient and whether low-dose initiation resulted in increased buprenorphine treatment retention or care engagement. Further, because not all urine drug tests included fentanyl, we were unable to assess the impact of fentanyl use on low-dose initiation. This study was performed at a single site and may not reflect feasibility and experiences initiating low-dose buprenorphine in other hospitals, particularly in community settings without availability of a specialized addiction consult service. Our study did not aim to compare different low-dose buprenorphine initiation protocols or compare low-dose initiation directly to traditional initiation. Results from an upcoming phase 2 clinical trial at the University of British Columbia (NCT04234191) evaluating a rapid low-dose initiation protocol compared to standard buprenorphine initiation will be essential to further evaluating these differences.[40] Instead, our intent was to describe clinical scenarios and highlight ways in which low-dose initiation may offer solutions, and to provide considerations for other clinicians to support low-dose initiation. Importantly, we recognize that the butrans patch may not always be available in all locations, and that some hospital pharmacies may not permit dividing doses of the butrans patch as we recommend (table 4). As low-dose initiation becomes more readily available we hope that these options will not limit these protocols. Future work should compare different low-dose initiation protocols including the use of parenteral formulations to support in-hospital low-dose initiation. In addition, research should expand to include particular patient populations such as pregnant patients and those using illicitly manufactured fentanyl.

Our findings have several important implications. In our experience, low-dose buprenorphine initiation requires far less intensive monitoring by nursing staff than standard initiations, which may facilitate its implementation in less-resourced hospitals. In most cases, low-dose initiation can be begin with standardized orders by those without specialized addiction training. The brief, targeted clinical guidance provided above covers most clinical situations. Hospitals can and should integrate low-dose buprenorphine initiation into their array of options for patients with OUD.

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REFERENCES

1. Weiss AJ. Opioid-Related Inpatient Stays and Emergency Department Visits by State, 2009–2014 #219. Accessed November 17, 2020. https://www.hcup-us.ahrq.gov/reports/statbriefs/sb219-Opioid-Hospital-Stays-ED-Visits-by-State.jsp.
2. Roehler DR, Guy GP Jr, Jones CM. Buprenorphine prescription dispensing rates and characteristics following federal changes in prescribing policy, 2017–2018: A cross-sectional study [published online ahead of print, 2020 May 25]. Drug Alcohol Depend 2020;213:108083. doi:10.1016/j.drugalcdep.2020.108083 [PubMed: 32505044]
3. Liebschutz JM, Crooks D, Herman D, et al. Buprenorphine treatment for hospitalized, opioid-dependent patients: a randomized clinical trial. JAMA Intern Med. 2014;174(8):1369–1376. doi:10.1001/jamainternmed.2014.2556 [PubMed: 25090173]
4. Englander H, Dobbertin K, Lind BK, et al. Inpatient Addiction Medicine Consultation and Post-Hospital Substance Use Disorder Treatment Engagement: a Propensity-Matched Analysis. J Gen Intern Med. 2019;34(12):2796–2803. doi:10.1007/s11606-019-05251-9 [PubMed: 31410816]
5. Comer S, Cunningham C, Fishman MJ, Gordon A, Kampman K, Langleben D, Nordstrom B, et al. National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use, 2015, 66.
6. Coe MA, Lofwall MR, Walsh SL. Buprenorphine Pharmacology Review: Update on Transmucosal and Long-acting Formulations. J Addict Med. 2019;13(2):93–103. doi:10.1097/ADM.0000000000000457 [PubMed: 30531584]
7. Antoine D, Huhn AS, Strain EC, et al. Method for Successfully Inducting Individuals Who Use Illicit Fentanyl Onto Buprenorphine/Naloxone. Am J Addict. 2021;30(1):83–87. doi:10.1111/ajad.13069 [PubMed: 32572978]
8. Shover CL, Falasinnu TO, Dwyer CL, et al. Steep increases in fentanyl-related mortality west of the Mississippi River: Recent evidence from county and state surveillance. Drug Alcohol Depend. 2020;216:108314. doi:10.1016/j.drugalcdep.2020.108314 [PubMed: 33038637]
9. 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;39(5):588–594. doi:10.1111/dar.13113 [PubMed: 32657496]
10. Klaire S, Zivanovic R, Barbic SP, Sandhu R, Mathew N, Azar P. Rapid micro-induction of buprenorphine/naloxone for opioid use disorder in an inpatient setting: A case series. Am J Addict. 2019;28(4):262–265. doi:10.1111/ajad.12869 [PubMed: 30901127]
11. Ward HB, Barnett BS, Suzuki J. Rapid transition from methadone to buprenorphine using naltrexone-induced withdrawal: A case report. Subst Abus. 2019;40(2):140–145. doi:10.1080/08897077.2019.1573776 [PubMed: 30888254]
12. Ahmed S, Bhivandkar S, Lonergan BB, Suzuki J. Microinduction of Buprenorphine/Naloxone: A Review of the Literature [published online ahead of print, 2020 Dec 30]. Am J Addict. 2020;10.1111/ajad.13135. doi:10.1111/ajad.13135
13. Moe J, O'Sullivan F, Hohl CM, et al. Short communication: Systematic review on effectiveness of micro-induction approaches to buprenorphine initiation. Addict Behav. 2021;114:106740. doi:10.1016/j.addbeh.2020.106740 [PubMed: 33352498]

14. Hämmig R, Kemter A, Strasser J, 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. Published 2016 Jul 20. doi:10.2147/SAR.S109919 [PubMed: 27499655]
15. Raheemullah A, Lembke A. Initiating Opioid Agonist Treatment for Opioid Use Disorder in the Inpatient Setting: A Teachable Moment. JAMA Intern Med. 2019;179(3):427–428. doi:10.1001/jamainternmed.2018.6749 [PubMed: 30640372]
16. Rozylo J, Mitchell K, Nikoo M, et al. Case report: Successful induction of buprenorphine/naloxone using a microdosing schedule and assertive outreach. Addict Sci Clin Pract. 2020;15(1):2. Published 2020 Jan 15. doi:10.1186/s13722-020-0177-x [PubMed: 31941547]
17. Caulfield MDG, Brar R, Sutherland C, Nolan S. Transitioning a patient from injectable opioid agonist therapy to sublingual buprenorphine/naloxone for the treatment of opioid use disorder using a microdosing approach. BMJ Case Rep 2020;13(3):e233715. Published 2020 Mar 25. doi:10.1136/bcr-2019-233715
18. Hamata B, Griesdale D, Hann J, Rezazadeh-Azar P. Rapid Micro-induction of Buprenorphine/Naloxone for Opioid Use Disorder in a Critically ill Intubated Patient: A Case Report. J Addict Med. 2020;14(6):514–517. doi:10.1097/ADM.0000000000000675
19. Robbins J, Eglander H, Gregg J. Buprenorphine Microdose Induction for the Management of Prescription Opioid Dependence: A Case Series in Primary Care. American Board of Family Medicine. 2020.
20. Azar P, Wong JSH, Jassemi S, et al. A Case Report: Rapid Micro-Induction of Buprenorphine/Naloxone to Administer Buprenorphine Extended-Release in an Adolescent With Severe Opioid Use Disorder. Am J Addict. 2020;29(6):531–535. doi:10.1111/ajad.13050 [PubMed: 32346944]
21. 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):601–604. doi:10.1111/ajad.12809 [PubMed: 30387894]
22. Weimer MB, Guerra M, Morrow G, Adams K. Hospital-based Buprenorphine Micro-dose Initiation [published online ahead of print, 2020 Sep 21]. J Addict Med. 2020;10.1097/ADM.0000000000000745. doi:10.1097/ADM.0000000000000745
23. Velez CM, Nicolaidis C, Korthuis PT, Englander H. "It's been an Experience, a Life Learning Experience": A Qualitative Study of Hospitalized Patients with Substance Use Disorders. J Gen Intern Med. 2017;32(3):296–303. doi:10.1007/s11606-016-3919-4 [PubMed: 27957661]
24. Englander H, Weimer M, Solotaroff R, et al. Planning and Designing the Improving Addiction Care Team (IMPACT) for Hospitalized Adults with Substance Use Disorder. J Hosp Med. 2017;12(5):339–342. doi:10.12788/jhm.2736 [PubMed: 28459904]
25. Englander H, Wilson T, Collins D, et al. Lessons learned from the implementation of a medically enhanced residential treatment (MERT) model integrating intravenous antibiotics and residential addiction treatment. Subst Abus. 2018;39(2):225–232. doi:10.1080/08897077.2018.1452326 [PubMed: 29595367]
26. Englander H, Mahoney S, Brandt K, et al. Tools to Support Hospital-Based Addiction Care: Core Components, Values, and Activities of the Improving Addiction Care Team. J Addict Med. 2019;13(2):85–89. doi:10.1097/ADM.0000000000000487 [PubMed: 30608265]
27. King C, Nicolaidis C, Korthuis PT, Priest KC, Englander H. Patterns of substance use before and after hospitalization among patients seen by an inpatient addiction consult service: A latent transition analysis. J Subst Abuse Treat. 2020;118:108121. doi:10.1016/j.jsat.2020.108121 [PubMed: 32972645]
28. Englander H, King C, Nicolaidis C, et al. Predictors of Opioid and Alcohol Pharmacotherapy Initiation at Hospital Discharge Among Patients Seen by an Inpatient Addiction Consult Service. J Addict Med 2020;14(5):415–422. doi:10.1097/ADM.0000000000000611 [PubMed: 31868830]
29. Collins D, Alla J, Nicolaidis C, et al. "If It Wasn't for Him, I Wouldn't Have Talked to Them": Qualitative Study of Addiction Peer Mentorship in the Hospital [published online ahead of print, 2019 Dec 12]. J Gen Intern Med. 2019;10.1007/s11606–019-05311–0. doi:10.1007/s11606-019-05311-0

30. Englander H, Gregg J, Gullickson J, et al. Recommendations for integrating peer mentors in hospital-based addiction care. Subst Abus 2020;41(4):419–424. doi:10.1080/08897077.2019.1635968 [PubMed: 31490736]

31. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009 Apr;42(2):377–81. [PubMed: 18929686]

32. Els C, Jackson TD, Kunyk D, et al. Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews. Cochrane Database Syst Rev. 2017;10(10):CD012509. Published 2017 Oct 30. doi:10.1002/14651858.CD012509.pub2 [PubMed: 29084357]

33. RStudio Team (2020). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA URL http://www.rstudio.com/.

34. Kinasz KR, Herbst ED, Kalapatapu RK. Case Report: Buprenorphine Induction Using Transdermal Buprenorphine in a Veteran With Opioid Use Disorder and Psychosis, Managing Precipitated Withdrawal. Mil Med. 2020;185(9–10):e1872–e1875. doi:10.1093/milmed/usaa068 [PubMed: 32314788]

35. Neumann AM, Blondell RD, Hoopsick RA, Homish GG. Randomized clinical trial comparing buprenorphine/naloxone and methadone for the treatment of patients with failed back surgery syndrome and opioid addiction. J Addict Dis. 2020;38(1):33–41. doi:10.1080/10550887.2019.1690929 [PubMed: 31774028]

36. Donroe JH, Holt SR, Tetrault JM. Caring for patients with opioid use disorder in the hospital. CMAJ. 2016;188(17–18):1232–1239. doi:10.1503/cmaj.160290 [PubMed: 27647616]

37. Lail P, Fairbairn N. Patients With Substance Use Disorders Leaving Against Medical Advice: Strategies for Improvement. J Addict Med. 2018;12(6):421–423. doi:10.1097/ADM.0000000000000432 [PubMed: 29939874]

38. Kimmel SD, Rosenmoss S, Bearnot B, Larochelle M, Walley AY. Rejection of Patients With Opioid Use Disorder Referred for Post-acute Medical Care Before and After an Anti-discrimination Settlement in Massachusetts. J Addict Med 2021;15(1):20–26. doi:10.1097/ADM.0000000000000693 [PubMed: 32675798]

39. Gregg J Health Affairs Podcast. Dying To Access Methadone. 2019. Available at: https://www.healthaffairs.org/doi/10.1377/hp20190626.899145. Accessed January 11, 2021.

40. Wong JSH, Nikoo M, Westenberg JN, 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. Addict Sci Clin Pract. 2021;16(1):11. Published 2021 Feb 12. doi:10.1186/s13722-021-00220-2 [PubMed: 33579359]

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)
Unknown	1 (1.5)
Ethnicity	
Not Hispanic or Latino	64 (94.1)
Hispanic	3 (4.4)
Unknown	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 prior to 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.

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 prior to the third, completed low-dose initiation.

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) 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. Taper methadone in partnership with patients. 2. 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. 3. 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. 4. 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.

Clinical Scenario (with references)	Low-dose Buprenorphine Initiation Practice Considerations
	b. Communicate with outpatient providers to ensure their understanding of and rationale for low-dose buprenorphine initiation.

Table 4:

Low-Dose Buprenorphine Initiation Protocol

A. Standard Protocol		
Initiation Day	**Dosing Schedule**	**Notes**
1	20 mcg buprenorphine transdermal patch x 24 hours	Patch on x 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[1]	Remove patch
B. Acute pain protocol		
Initiation Day	**Dosing Schedule**	**Notes**
1	20 mcg buprenorphine transdermal patch x 24 hours	Patch on x 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[3]
6	increase bup/nx as needed for pain NTE 24 mg/24 hours[2]	
7		Remove patch
C. Transition from Methadone protocol		
Initiation Day	**Dosing Schedule**	**Notes**
1	20 mcg buprenorphine transdermal patch x 24 hours	Patch on x 7 days; Continue methadone[4]
2	20 mcg buprenorphine transdermal patch x 24 hours	No SL bup/nx; Continue methadone
3	patch + 1 mg SL bup/nx x 1 dose	Continue methadone vs. start methadone taper based on patient preference[5]
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[1]	

[1] Final dose dependent on patient need and based on medical assessment

[2] Final dose dependent on patient need and based on medical assessment in split dosing

[3] Taper schedule dependent on individual patient case and medical assessment

[4] Low-dose buprenorphine initiation should be started once methadone dose 80 mg or less

[5] We find patient input on this decision supports success.

bup/nx, buprenorphine/naloxone either tablet or film; NTE, not to exceed; SL sublingual