Low Dose Buprenorphine Induction With Full Agonist Overlap in Hospitalized Patients With Opioid Use Disorder: A Retrospective Cohort Study

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Objective: To describe the outcomes of buprenorphine/naloxone low dose induction with overlap of full opioid agonists among hospitalized patients with opioid use disorder (OUD) as an alternative to standard induction strategies.

Methods: Retrospective cohort study of patients with OUD who were admitted to the hospital over a 1-year period and initiated ono buprenorphine using initial doses of 0.5 mg and gradually increased while the patient remained on full agonists. Descriptive variables included basic demographics, reason for switching to buprenorphine, baseline opioid and morphine equivalent dose. The primary outcome was a successful transition defined by the patient leaving the hospital with a buprenorphine prescription. Bivariate analysis identified factors associated with unsuccessful medication transitions. Secondary outcomes included reported withdrawal symptoms and 30 day follow up to an outpatient buprenorphine program.

Results: Sixty two patients underwent low dose with overlap induction during the study period. Fourteen patients were on methadone for OUD before hospital admission. Fifty one patients (82%) successfully left the hospital with a prescription for buprenorphine. Factors associated with lower likelihood of success included older age, transitioning due to discharge placement needs and presence of withdrawal symptoms during the transition. Overall, 66% (N = 23) of patients referred within the same health care system followed up within 30 days.

Conclusions: Low dose inductions with overlap of full opioid agonists were largely successful in transitioning hospitalized patients from full agonist opioids to buprenorphine. However, there were several factors associated with lower likelihood of success. Future work could focus on treatment of withdrawal symptoms and system-level changes ensuring patient-centered medication decisions.

Key Words: buprenorphine, low dose induction, opioid use disorder

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Buprenorphine is a partial opioid agonist medication used to treat opioid use disorder (OUD). Patients with OUD on buprenorphine have lower mortality rates as well as lower Hepatitis C and HIV transmission compared to patients not on treatment.[1–4] Buprenorphine can be prescribed in an office based setting or dispensed through an opioid treatment program. Although medications, including buprenorphine, are the gold standard of treatment for patients with OUD, there remains a treatment gap between patients who would benefit from these medications and patients who actually receive them.[5]

Recent evidence suggests that starting patients on buprenorphine during hospitalizations for acute medical issues can lead to successful linkage with outpatient treatment.[6–9] Traditional protocols for starting buprenorphine, however, require careful attention to timing.[10] Due to buprenorphine's pharmacokinetics (high affinity for the mu opioid receptor with only partial agonism), it is advised that patients wait until they are in mild-to-moderate withdrawal before taking the first dose of buprenorphine. Initiating induction prematurely and at standard induction doses risks precipitating sudden, potentially severe, opioid withdrawal symptoms. Waiting for spontaneous opioid withdrawal, however, may not be acceptable or appropriate for patients in the hospital, especially those who are having acute pain and requiring opioid pain medications. In addition, patients who have been on methadone for OUD are often advised to taper their dose to 30 to 40 mg per day and then wait 72 hours before their first dose of buprenorphine.[11] This process may take weeks or months, depending on the starting dose of methadone, and can increase the risk of returning to non-prescribed opioid use as the dose is lowered.

The need to transition from higher-dose and/or long-acting full agonist opioids to buprenorphine may present in multiple situations. Common scenarios include: (1) patients being treated for acute pain with full agonist opioids in the context of hospitalization for severe trauma or after major surgeries but preferring buprenorphine in the long term and (2) those that either require or request switching from methadone for OUD to buprenorphine during a hospitalization (for example due to patient preference, prolonged corrected QT interval, or high risk for respiratory depression). Unjustly, there is also a substantial barrier to postacute care placement for patients on methadone, which can prompt consideration of transition to buprenorphine.[12,13] Depending upon the individual's degree of tolerance and physiologic dependence, comorbid pain, the duration of required abstinence, and other

factors, the "washout" period of a standard induction can be a significant barrier to achieving a successful induction and they may benefit from a modified approach to buprenorphine initiation.[14]

There has been a recent trend of utilizing low dose buprenorphine inductions (also called micro-induction or overlap method) as an alternative to standard induction strategies, allowing patients to initiate buprenorphine without stopping full agonists or undergoing withdrawal. The strategy of utilizing low dose buprenorphine as a tool to help transition patients on full agonists was first described in the literature in 2011,[15] and then gained attention when Hemmig et al described a case series of 2 patients in 2016.[16] In that report, one patient was transitioning from heroin and one from diacetylmorphine (pharmaceutical grade heroin) and methadone. Both patients started at doses of 0.2mg of buprenorphine and the transitions took 5 and 29 days, respectively. Variations have emerged, all utilizing low initial buprenorphine doses then gradually increasing while the patient continues on full agonist until buprenorphine reaches a therapeutic dose. Although this transition process is becoming more prevalent clinically, and approaches are being described in specific contexts such as inpatient, outpatient and among patients on long term opioids for chronic pain, the existing literature is limited. Button et al published the first retrospective cohort analysis (N = 72) in 2021, which broadens the body of work from small case series.[16–21] We describe here a series of hospitalized patients who were transitioned from full opioid agonists to buprenorphine using a low dose with overlap of full agonist protocol and also identify risk factors for unsuccessful low dose inductions. The aims of this study are threefold: (1) contribute to a higher level of understanding on the topic with a substantial cohort analysis, (2) identify factors associated with unsuccessful low dose inductions, which is currently lacking in the literature, and (3) documented post discharge buprenorphine follow up within 30 days.

METHODS

Study Design and SETTING

We conducted a retrospective observational cohort study at Harborview Medical Center in Seattle WA, a public, urban safety-net hospital and level 1 trauma center.

Sample Selection

Eligible patients were adults with a diagnosis of OUD seen by the inpatient Addiction Consult Service (ACS) and initiated on buprenorphine using a low dose with full opioid agonist overlap approach between June 1, 2019 and May 31, 2020. The ACS is a multidisciplinary team available to all inpatient services and has a focus on patients with OUD. Cases were identified using 2 sources. The ACS maintains a registry of patients attempting microdose inductions. To check for patients inadvertently omitted from the registry, the electronic health record was queried for all hospitalized patients who had received a buprenorphine dose of 0.5 mg during the study period. These charts (N = 140) were then reviewed by a member of the research team to determine if the patient met the study inclusion criteria. Common reasons for exclusion among patients on this list included management solely by a non-ACS team, and buprenorphine used for pain rather than for OUD.

Low Dose With Overlap Procedure

A standard protocol was used for the low dose with overlap induction, which was adapted from the University of British Columbia[22] and utilized sublingual buprenorphine/naloxone, either in film or tablet formulation. The initial dose was 0.5 mg of buprenorphine administered once on the first day and the dose gradually increased over seven days (Table 1). The full agonist opioids were continued throughout the transition period, and then discontinued or tapered (as deemed clinically appropriate by the primary team) once the patient reached a therapeutic buprenorphine/naloxone dose. Although this standard protocol was utilized for most patients, adjustments were made based on clinical needs and patient preference.

Data Collection and Measures

Data was abstracted manually from the electronic medical record and entered in to a central database[23] by 2 authors. Descriptive characteristics were gathered from the demographics information in the electronic medical record and review of the ACS notes. Variables included age, sex, race, ethnicity, presence of concurrent non-opioid substance use disorders, length of stay in the hospital, reason for low dose induction as documented in the consult notes and details around full-opioid agonist treatment, including any full agonist opioids prescribed at discharge. Variables were chosen based on prior low dose induction literature and clinical experience.[21,24] Morphine equivalent doses were calculated using the Opioids Dosage Conversion iPhone application.[25] Details of the induction process were gathered from the medication administration record and clinical documentation by the ACS, bedside nurses and the primary team. The low dose with overlap duration was defined as the number of days from date of initial buprenorphine microdose (0.5 mg) until a stable buprenorphine dose was reached or the patient discharged. All study procedures were approved by the University of Washington Institutional Review Board.

Outcomes

The primary outcome was successful transition on to buprenorphine, defined as leaving the hospital with a buprenorphine prescription and a plan for outpatient buprenorphine

TABLE 1. Microdose with Overlap Protocol

	Dose of Buprenorphine*	Full Agonist
Day 1	0.5 mg once	Baseline dose
Day 2	0.5 mg BID	Baseline dose
Day 3	1 mg BID	Baseline dose
Day 4	2 mg BID	Baseline dose
Day 5	4 mg BID	Baseline dose
Day 6	8 mg Once	Baseline dose
Day 7*	8 mg AM/4 mg PM	Baseline dose
Day 8	8 mg BID	None

*Buprenorphine/naloxone films or tablets were utilized. Buprenorphine specific doses are reported here for simplicity.

follow up. This definition was chosen to capture all situations where the clinical team intended to continue buprenorphine after an attempted low dose with overlap induction and is consistent with the small body of existing literature.[21,24,26] Patients discharged with buprenorphine as well as full agonists for ongoing acute pain with a plan to taper the full agonists at home were included as successful, as were patients discharged partway through the induction protocol but with instructions and a buprenorphine prescription to complete the transition at home. Patients who attempted low dose with overlap induction but did not leave the hospital with a buprenorphine prescription were defined as unsuccessful.

Clinically relevant included (1) any documented withdrawal symptoms during the low dose with overlap induction and (2) attending a follow up appointment for buprenorphine treatment within 30 days of discharge (restricted to patients referred within the same health care system as we were not able to track follow up for patients referred outside of our system). Of note, clinical notes were reviewed for mention of withdrawal symptoms, but there was no formal tracking or documentation of withdrawal symptoms, such as with a clinical opioid withdrawal scale. Withdrawal symptoms were identified as a secondary outcome as well as an independent variable when looking for predictors of unsuccessful transition.

Statistical Analysis

Demographic characteristics and outcomes were reported for the entire cohort. The characteristics of patients who successfully transitioned to buprenorphine compared to those who were unsuccessful were compared with bivariate analyses using chi-squared, Student *T* test and Wilcoxon-Mann-Whitney tests. Statistical analysis was completed using Stata, version 16 (College Station, TX).[27]

RESULTS

We identified 62 patients who attempted to initiate buprenorphine using a low dose with overlap induction during the 12-month study period. Forty patients were identified through the patient registry and an additional 22 through EHR query. Our cohort included 40% women, nearly two-thirds were under age 50 and relatively few individuals were identified as belonging to a racial/ethnic minority group (Table 2). The overwhelming majority (82%) had a concurrent nonopioid substance use disorder. The median hospital length of stay was 19.5 days (IQR 13–39 days, mean 30 days). Nearly one-quarter of patients were on methadone for OUD at the time of hospital admission and two-thirds were on methadone at the time of buprenorphine initiation. The most common reasons

TABLE 2. Patient Characteristics and Outcomes

Variable	Successful (n = 51)	Unsuccessful (n = 11)	Total (N = 62)	*P*
Age in years, mean (range)	42 (21–69)	53 (38–67)	44 (21–69)	<0.01
Sex				0.08
M	33 (65%)	4 (36%)	37 (60%)	
F	18 (35%)	7 (64%)	25 (40%)	
Ethnicity				0.45
Hispanic	2 (4%)	1 (9%)	3 (5%)	
Not Hispanic	49 (96%)	10 (91%)	59 (95%)	
Race/Ethnicity*				0.23
White	46 (90%)	8 (73%)	54 (87%)	
Black/African American	3 (6%)	2 (18%)	5 (8%)	
Hispanic	2 (4%)	1 (9%)	3 (5%)	
Asian	0 (0%)	0 (0%)	0 (0%)	
American Indian/Alaska Native	4 (8%)	3 (27%)	7 (11%)	
Other	1 (2%)	0 (0%)	1 (2%)	
Length of stay in days, median (SD), range	28 (24) 4–106	43 (45) 6–156	30 (29) 4–156	0.31
Concurrent non-opioid substance use disorder	41 (80%)	10 (91%)	51 (82%)	0.41
Reason for transition				<0.01
Post-hospital placement	8 (15%)	6 (55%)	14 (23)	
Patient preference/Request	35 (69%)	2 (18%)	37 (60%)	
Patient requests to switch from methadone for OUD to buprenorphine	6 (12%)	1 (9%)	7 (11%)	
Safety concerns*	2 (4%)	2 (18%)	4 (6%)	
Full Agonist at time of switch†				0.59
Methadone started during hospitalization	24 (47%)	4 (36%)	28 (45%)	
Methadone for OUD treatment on admission	9 (18%)	5 (45%)	14 (23%)	
Oxycodone	26 (51%)	3 (27%)	29 (47%)	
Hydromorphone	29 (57%)	4 (36%)	33 (53%)	
Fentanyl	8 (16%)	1 (9%)	9 (15%)	
Other	2 (4%)	0 (0%)	2 (3%)	
Full agonist MED, median (SD), range	217 (239) 12–1065	375 (502) 59–1505	228 (313) 12–1505	0.22
Any withdrawal symptoms reported during transition N (%)	16 (31)	7 (64)	23 (37)	0.03

*Safety concerns included: long QT/arrhythmia (2) prior respiratory arrest on methadone (1) somnolence (1) constipation (1).

†Not mutually exclusive.

identified for transitioning to buprenorphine were acute pain requiring full agonist opioids in the hospital but a personal preference for buprenorphine long-term (61%) and a desire to facilitate post-discharge placement (27%).

Overall, 82% (N = 51) of patients successfully transitioned on to buprenorphine. The duration of the microdose protocol among successful transitions ranged from 2 to 35 days with a mean of 8 (median 7, IQR 4–9). Withdrawal symptoms were identified among 23 patients (39%); most of these were described as minor and included anxiety, diaphoresis and headaches. Just under half (N = 30, 48%) of all patients were discharged with full opioid agonists, including 23 (37%) who were discharged on both buprenorphine and full agonists. Of the 35 successful patients referred within our health care system, 23 (66%) followed up within 30 days of hospital discharge.

Table 2 compares characteristics of patients who successfully transitioned to those who did not. Characteristics associated with unsuccessful transitions included older age (<0.01), reporting any withdrawal symptoms during transition (0.03) and switching to buprenorphine for post-hospital placement (<0.01).

DISCUSSION

To our knowledge, this is one of the largest cohorts describing the characteristics of hospitalized patients with OUD transitioned from full agonist opioids to buprenorphine using an induction strategy of low dose buprenorphine with overlap of full agonist (referred to here as, "low dose with overlap"). We demonstrate that this approach resulted in a high proportion of patients leaving the hospital on buprenorphine, with a prescription and a plan to continue with outpatient treatment.

A minority of patients experienced withdrawal symptoms and two-thirds of those referred to the same institution linked to outpatient care within 30 days of discharge.

Our results bolster the small but growing body of literature that supports using a low dose with overlap approach for transition to buprenorphine. Most existing descriptions of low dose inductions in hospitalized patients have consisted of small case series using various protocols. Klaire and colleagues described a three-day protocol used to successfully transition 2 hospitalized patients from full agonist opioids to buprenorphine.[28] Terasaki and colleagues identified 3 hospitalized patients treated with methadone (40–100 mg per day) who successfully achieved therapeutic buprenorphine doses using a one-week protocol.[21] Some institutions have suggested using transdermal buprenorphine as part of low dose regimens.[29] The current study adds both a large number of cases and is also the first to describe the percentage of successful transitions and factors associated with unsuccessful transition attempts.

For patients who are admitted for trauma or other conditions requiring surgery, full agonist opioids may be required for both pain and withdrawal management.[30,31] Low dose with overlap induction provides an alternative to abrupt full agonist discontinuation. Apart from withdrawal symptoms reported by a minority of patients, we did not identify any documented adverse events associated with the transitions, and over the one-year study period a substantial number of patients chose to attempt this approach.

Characteristics associated with unsuccessful transitions included older age, documented withdrawal symptoms and provider-driven as opposed to patient-driven reason for transition (ie, for the purposes of post hospital placement). Although age is nonmodifiable, more aggressive treatment of withdrawal symptoms during the transition period and avoiding unilateral initiation of low-dose buprenorphine transition may increase the likelihood of successful transition to buprenorphine. In our clinical experience, patient motivation and confidence in the process are important predictors of success. This is borne out by our data, which demonstrated that 43% of patients who attempted low dose with overlap to facilitate posthospital placement were unsuccessful versus just 5% of those who were started on full agonist opioids for pain but declared a preference for buprenorphine and elected to transition prior to discharge. Additionally, among patients who were on methadone for OUD at admission but requested a switch to buprenorphine, only 9% were unsuccessful, again demonstrating that patient motivation is likely a major factor in success of this method.

Importantly, our findings should prompt a closer look at how to facilitate ongoing methadone treatment when patients are discharged to postacute care facilities. Unfortunately, patients with OUD, and specifically patients taking methadone, are often discriminated against and refused from these facilities.[13] Unilaterally initiating low-dose buprenorphine transition for the sake of discharge placement is not in line with best practice guidelines for the treatment of OUD.

Our study has several important limitations. Data was retrospectively obtained from the electronic health record, where information could have been missing or incorrectly documented. There was also no control group for comparison. The study was conducted at a single public academic medical center that operates as the trauma and burn center for a large geographic region, potentially limiting the generalizability of our results. We utilized a standard low dose with overlap protocol, but there was room for flexibility based on clinical needs and patient preference. Future work could examine more closely the cases where the protocol was adjusted. The decision to offer this approach was at the discretion of the ACS attending and could have introduced selection bias. A fairly large proportion of patients we defined as successful left the hospital with a prescription for a full opioid agonist to treat ongoing acute pain, and in many cases, we could not assess the success of any subsequent full opioid taper. We were not able to report on the exact buprenorphine dose of each patient when they left the hospital, but we do know that the median days of low dose induction competed in the hospital was 7. This suggests that most patients likely reached a dose of at least 12 mg per day. Although it is promising that we did not identify severe withdrawal symptoms during chart review, we did not systematically assess for adverse events and patients were permitted to discontinue the transition at their discretion. Future studies should continue to assess the potential for adverse events during these transitions.

Given our relatively small number of patients and outcomes, as well as the exploratory nature of the study, we opted not to perform multivariable regression analyses. For the secondary outcome of linkage with outpatient care, we were only

able to track follow up for patients who were referred within our medical system.

CONCLUSIONS

In conclusion, transition from full agonist opioids to buprenorphine using low dose with overlap of full opioid agonist inductions appears to be feasible for the majority of patients in an inpatient setting. However, there were several factors associated with a decreased likelihood of success, the most striking of which was whether the decision to transition to buprenorphine was patient or provider driven. Further research should work to identify patients who are most likely to benefit from a low dose with overlap induction and further assess the safety of this approach. Policy work should continue to focus on improving the ability to offer all appropriate medications for OUD in post-acute care settings.

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