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Short communication

Adapting low-dose buprenorphine induction to meet patient needs: A pilot study

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ABSTRACT

Introduction: Low-dose buprenorphine induction (LDBI) has been proposed to initiate buprenorphine in patients who are taking full opioid agonists in order to limit the risk of precipitated withdrawal. The objective of this study was to understand how real-world patient-specific adjustments in LDBI protocols impacted success rates in buprenorphine conversion.

Methods: This case series identified patients seen by the Addiction Medicine Consult Service at UPMC Presbyterian Hospital who were started on LDBI with transdermal buprenorphine followed by sublingual buprenorphine-naloxone between April 20, 2021, and July 20, 2021. The primary outcome was successful induction of sublingual buprenorphine. Characteristics of interest included total morphine milligram equivalents (MME) in the 24 hours prior to induction, MME during each day of induction, total time of induction, and final daily maintenance buprenorphine dose.

Results: Of the 21 patients included for analysis, 19 (91%) successfully completed LDBI and converted to a maintenance buprenorphine dose. Median (IQR) opioid analgesia utilization in the 24 hours prior to induction was 113 MME (63–166 MME) in the converted group and 83 MME (75–92 MME) in the group that did not convert.

Conclusions: Transdermal buprenorphine patch followed by sublingual buprenorphine-naloxone resulted in a high success rate for LDBI. Patient-specific adjustments may be considered in order to effect a high success rate of conversion.

1. Introduction

The opioid overdose crisis is a serious public health concern, with drug overdose deaths in the United States rising by 30% in 2020 (CDC/National Center for Health, 2021). A gold standard treatment option for opioid use disorder (OUD) is buprenorphine, a partial opioid agonist that can reduce both cravings and mortality (Gowing et al, 2017; Mattick et al, 2014; Santo et al 2021; Sordo et al, 2017). In comparison to patients receiving medications for opioid use disorder (MOUD), patients not receiving MOUD are 8.1 times more likely to die from an overdose (Ma et al., 2019).

Traditional buprenorphine induction for the treatment of OUD requires the patient to experience mild-to-moderate withdrawal before taking their first dose of buprenorphine (Shulman et al, 2019). Initiating buprenorphine too early has the risk of precipitating withdrawal, which can make patients even more uncomfortable with the cessation of illicit opioid use.

Low-dose buprenorphine induction (LDBI) is based on the principle that overlapping induction of buprenorphine with ongoing use of opioids is possible without precipitating withdrawal (Ahmed et al, 2021; De Aquino et al, 2021). The doses used for LDBI are typically much lower than for traditional induction. Institutions differ in their use of transdermal, intravenous, buccal, and sublingual buprenorphine (Robbins et al., 2021; Saal & Lee, 2020; Thakrar et al., 2022; Weimer et al., 2021). Buprenorphine formulation can differ based on provider preference, patient preference, and hospital formulary.

Literature surrounding outcomes of LDBI is limited. A retrospective observational study reported that 38 of 41 cases successfully transitioned to sublingual buprenorphine via transdermal buprenorphine from full-agonist opioids (Baumgartner et al., 2022). The majority (59%) of transitions were fairly well-tolerated, while an additional 32% were fairly tolerated (Baumgartner et al., 2022). Additional retrospective cohort analyses found that 81.9% and 82% of low-dose buprenorphine inductions were successful (Bhatraju et al., 2021; Button et al., 2022). These studies followed specific protocols based on various previously

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published guidance. Baumgartner et al employed a 3+ day protocol that stopped all opioid agonists by day one. Button et al reported a standard protocol of 7 days while Bhatraju et al modeled their protocol from the University of British Columbia's protocol, which lasted up to 7 days in length (Hammig et al, 2016). At our hospital, we follow a three-day induction period, in accordance with the recommendations of Raheemallah and Lembke (2019). However, we frequently adjust the length of induction to respond to patient needs, including their concerns around precipitated withdrawal and inadequate pain management. In addition, this protocol recommends taper of full agonists prior to and during LDBI.

Therefore, our first objective was to demonstrate success and failure of LDBI among all patients, including those who may receive longer or patient-adjusted inductions compared to previously published protocolized suggestions. Our second objective was to evaluate if a potential relationship exists between morphine milligram equivalents (MME) prior to induction and 1) success of induction and 2) days of induction. We sought to understand if there were any trends towards an MME limit that would impact the success of LDBI, in order to see if taper prior to initiation is warranted. We hypothesized that patients would successfully transition to buprenorphine regardless of MME received prior to induction and that people who had higher MME prior to induction would not trend towards having a longer LDBI transition.

2. Material and methods

This observational study involving a case series was conducted at a large, tertiary care academic medical center. We sought to retrospectively review patients seen by the Addiction Medicine Consult Service (AMCS) at UPMC Presbyterian Hospital during an inpatient stay between April 20, 2021, and July 20, 2021 who were started on LDBI during their hospitalization. The AMCS is comprised of addiction medicine physicians, an advanced practice provider, social workers, and certified recovery specialists.

Low-dose buprenorphine induction was defined as initiation of transdermal buprenorphine patch before transition to sublingual buprenorphine films for patients simultaneously receiving opioid agonists. The basic structure of the regimen used is as follows: day 1- 20mcg/hr transdermal buprenorphine patch applied in the morning, for at least 24 hours; day 2- sublingual buprenorphine/naloxone 2–0.5 mg every 2–4 hours for four doses; day 3- discontinue patch and begin maintenance dosing, usually sublingual buprenorphine/naloxone 8–2 mg twice daily. This regimen was subject to adjustments in timing and dosages as determined by attending physician or at request of patient.

Retrospective chart review was used to collect baseline patient characteristics and outcomes data. Data extraction was performed by ZAK and secondarily reviewed by PJR. Data were stored on a standardized Excel sheet on a secure network. Patients were identified for inclusion from an internal consult service database. Patients were not excluded from LDBI based on length of stay. Baseline patient characteristics and outcomes were reported as descriptive statistics. The primary outcome of interest was successful LDBI, defined as greater than or equal to 24 hours on maintenance sublingual buprenorphine, or receiving a discharge prescription at maintenance dose. Maintenance sublingual buprenorphine was defined as a patient's final buprenorphine dose at discharge or highest dose of buprenorphine achieved after induction. Opioid-related characteristics included initial buprenorphine patch dose; transition from methadone; route of opioid administration prior to transition (oral/intravenous); and total MME in the 24 hours prior to start of induction, calculated based on receipt of all intravenous and oral opioids in the 24 hours prior to transdermal buprenorphine patch application. MME was calculated according to the Centers for Disease Control and Prevention (CDC) recommended equivalency guidance (Centers for Disease Control and Prevention, 2021). Additional characteristics included time of transition, measured by days from start of transdermal buprenorphine patch to first day of sublingual buprenor-

Table 1
Demographic and opioid-related characteristics among patients attempting low-dose buprenorphine induction.

Demographic characteristics	
Overall	n=21
Sex, n (%)	
Male	8 (38%)
Race, n (%)	
White	19 (91%)
Black	1 (5%)
Other	1 (5%)
Age (years), median (IQR)	39 (31–47)
Opioid-related characteristics	
Overall	n=21
Time between admission and AMCS (days), median (IQR)	1 (1 – 1)
Time between admission and patch application (days), median (IQR)	6 (1 – 12)
Initial buprenorphine patch dose (mcg/hr), n (%)	1 (5%)
0 (0%)	
5	19 (90%)
10	1 (5%)
20	
40	
Transition from methadone, n (%)	5 (24%)
Opioid route prior to transition, n (%)	20 (95%)
Oral	11 (52%)
Intravenous	
MME in 24-hours prior to patch application, median (IQR)	92 (66 – 160)
Opioid-related characteristics of converted group	
Overall	n=19
Time of transition (days), median (IQR)	4 (3 – 5)
Taper during transition period, n (%)	4 (21%)
MME per 24-hours during transition, median (IQR)	98 (65 – 134)
	90 (46 – 117)
Day 1 (n=19)	60 (0 - 90)
Day 2 (n=19)	68 (8 - 96)
Day 3 (n=16)	113 (0 - 129)
Day 4 (n=13)	128 (107 – 157)
Day 5 (n=7)	110 (89 – 116)
Day 6 (n=4)	90 (86 – 117)
Day 7 (n=3)	118 (118 – 118)
Day 8 (n=3)	114 (114 – 114)
Day 9 (n=1)	0 (0–0)
Day 10 (n=1)	
Day 11 (n=1)	
Final daily dose buprenorphine (mg), n (%)	1 (5%)
	3 (14%)
2	14 (74%)
4	1 (5%)
16	
24	

Patient	Days of transition										
	1	2	3	4	5	6	7	8	9	10	11
1		2 mg- 0.5 mg									
		2 mg- 0.5 mg									
		2 mg- 0.5 mg	8 mg- 2 mg	8 mg- 2mg	8 mg- 2 mg	8 mg- 2 mg					
		2 mg- 0.5 mg	8 mg- 2 mg	8 mg- 2 mg	8 mg- 2 mg	8 mg- 2 mg					
	20 mcg	20 mcg	20 mcg	20 mcg	20 mcg	20 mcg					
	63 MME	78.2 MME	0 MME	0 MME	0 MME	0 MME					
2				2 mg							
		2 mg		2 mg	8 mg						
	20 mcg	2 mg		4 mg	8 mg						
	113 MME	55 MME	53 MME	23 MME	0 MME						
3				2 mg- 0.5 mg							
				2 mg- 0.5 mg							
				2 mg- 0.5 mg							
				2 mg- 0.5 mg	8 mg- 2 mg						
	20 mcg	20 mcg	20 mcg	20 mcg	8 mg- 2 mg						
	15 MME	38 MME	15 MME	8 MME	0 MME						
4		2 mg- 0.5 mg									
		2 mg- 0.5 mg									
	20 mcg	20 mcg									
	83 MME	15 MME									
5						2 mg					
		2 mg- 0.5 mg		2 mg- 0.5 mg		2 mg					
		2 mg- 0.5 mg	4 mg- 1 mg	4 mg- 1 mg	6 mg- 1.5 mg	2 mg	8 mg				
	20 mcg	20 mcg	4 mg- 1 mg	6 mg- 1.5 mg	6 mg- 1.5 mg	2 mg	8 mg				
	115 MME	113 MME	90 MME	0 MME	0 MME	0 MME	0 MME				
6										2 mg- 0.5 mg	
										2 mg- 0.5 mg	
										2 mg- 0.5 mg	
	20 mcg	20 mcg	20 mcg	20 mcg	20 mcg	20 mcg	20 mcg	20 mcg	20 mcg	20 mcg	8 mg- 2 mg
	98 MME	145 MME	96 MME	123 MME	145 MME	143 MME	122 MME	145 MME	118 MME	114 MME	0 MME
7				2 mg- 0.5 mg							
	40 mcg	40 mcg	40 mcg	2 mg- 0.5 mg	8 mg- 2 mg						
	30 mg	30 mg	30 mg	40 mcg	40 mcg						
	240 MME	240 MME	240 MME	0 MME	0 MME						
8				2 mg- 0.5 mg							
				2 mg- 0.5 mg							
				2 mg- 0.5 mg	8 mg- 2 mg						
	20 mcg	20 mcg	20 mcg	20 mcg	20 mcg						
	90 MME	90 MME	91 MME	68 MME	0 MME						
9			2 mg- 0.5 mg								
			2 mg- 0.5 mg								
			2 mg- 0.5 mg								
			2 mg- 0.5 mg	8 mg- 2 mg							
	20 mcg	20 mcg	20 mcg	8 mg- 2 mg							
	60 MME	30 MME	0 MME	0 MME							
10				2 mg							
				2 mg	4 mg						
	5 mcg	10 mcg	20 mcg	20 mcg	4 mg						
	72 MME	64 MME	16 MME	8 MME	0 MME						
11				2 mg							
				2 mg							
	20 mcg	20 mcg		2 mg	8 mg						
	5 mg	20 mcg	20 mcg	2 mg	8 mg						
	5 mg	5 mg	20 mcg	40 mcg	40 mcg						
	152 MME	64 MME	80 MME	96 MME	0 MME						
12							2 mg- 0.5 mg				
							2 mg- 0.5 mg				
							2 mg- 0.5 mg				
							2 mg- 0.5 mg	8 mg- 2 mg			
	20 mcg	20 mcg	20 mcg	20 mcg	20 mcg	20 mcg	20 mcg	8 mg- 2 mg			
	66 MME	161 MME	89 MME	82 MME	113 MME	113 MME	68 MME	90 MME			
13		20 mcg				2 mg					
	20 mcg	20 mcg	40 mcg	40 mcg	40 mcg	40 mcg					
	105 MME	90 MME	90 MME	68 MME	113 MME	90 MME					
14		2 mg- 0.5 mg									
		2 mg- 0.5 mg									
	20 mcg	20 mcg	4 mg- 1 mg								
	116 MME	113 MME	0 MME								
15	2 mg- 0.5 mg										
	2 mg- 0.5 mg										
	2 mg- 0.5 mg										
	2 mg- 0.5 mg										
	2 mg- 0.5 mg	8 mg- 2 mg									
	20 mcg	8 mg- 2 mg									
	0 MME	0 MME									
16							4 mg- 1 mg				
							2 mg- 0.5 mg	8 mg- 2 mg			

Fig. 1. Patient induction schedules.

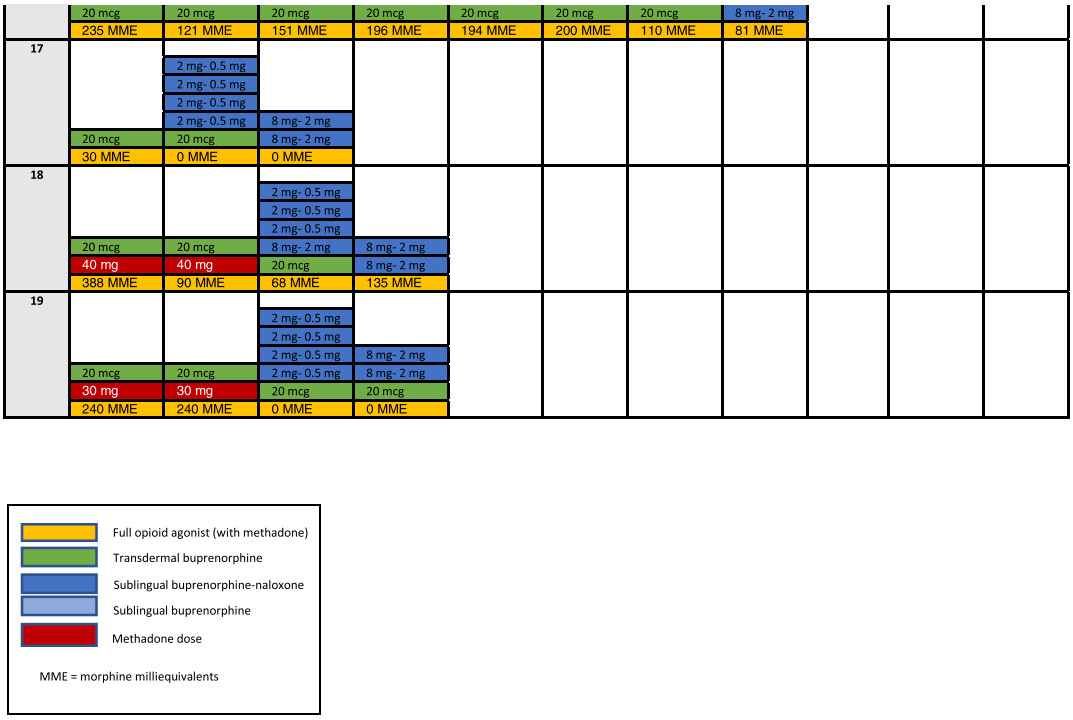

Fig. 1. Continued

phine maintenance dose; taper of full opioid agonists; total MME per 24 hours during transition; and final daily maintenance dose of sublingual buprenorphine. Taper of full opioid agonists during induction transition period was defined as a decrease in medication dosage or frequency indicated by order modification by a provider. MME per 24 hours during transition was collected for only the group of patients who successfully induced.

This project was approved by the Institutional Review Board at the University of Pittsburgh.

3. Results

Of the 21 patients included for analysis and initiated on LDBI, 19 (91%) converted successfully and two did not convert. Thirteen (62%) patients were female, 19 (91%) were white, and the median age was 39 years (Table 1). The median time between admission and addiction medicine consultation was 1 day (IQR 1–1 day) and median time between admission and patch application was 6 days (1–12 days).

Fig. 1 provides a summary of each patient's daily buprenorphine dose and full opioid agonist MME during transition. Eighteen of the 19 patients were discharged with a prescription for buprenorphine and 10 of 19 were discharged with a full agonist opioid prescription. The initial transdermal buprenorphine dose was 20 mcg/hr in 19 (91%) patients, while one patient was initiated on 5 mcg/hr and one patient on 40 mcg/hr. Five (24%) patients in the cohort were on methadone, which was initiated for opioid withdrawal management; all five successfully converted to buprenorphine. The majority of patients (95%) received oral opioids prior to transition, while approximately half (52%) received intravenous opioids. In the group that converted, the median MME utilization (IQR) in the 24 hours prior to patch application was 113 MME (63–166 MME), compared to 83 MME (75–92 MME) in the group that did not convert. The median length of time for transition was 4 days. Four (21%) patients had a taper of full opioid agonist during the low-dose induction. The median MME per 24 hours during the transition time per person ranged from 0 MME to 128 MME. At the end of the transition, 14 (74%) had a final daily maintenance dose of sublingual buprenorphine of 16 mg.

4. Discussion

This observational study found that adapting a low-dose buprenorphine induction protocol to patient preference and initiating induction regardless of opioid analgesia MME can result in high induction success rates.

Our approach to LDBI has differences to note from previously published practice in regards to average time to induction. The median time of transition in this study of 4 days is longer than some previously published literature that cites transition times between one and four days (Azar et al., 2022; Baumgartner et al., 2022). However, one case series that specifically used transdermal buprenorphine for LDBI noted transition times of up to seven days (Saal & Lee, 2020). In addition, our LDBI approach illustrated variable transition times, with patients ranging from two to 11 days of total transition; whereas much of the previous literature reports patients with a transition time within a small window, for example three to four days (Baumgartner et al., 2022).

Given the uneven sample sizes between the converted and did not convert groups and overall low sample size, we were unable to demonstrate a correlation between MME prior to transition and LDBI success. The MME requirement in the 24 hours prior to patch application was lower in the two patients who did not transition successfully, suggesting there is likely no correlation between baseline MME requirement and transition success. The high baseline MME in our study is in concordance with previous studies, also supporting the lack of an MME threshold prior to transition (Baumgartner et al., 2022; Bhatraju et al 2021; Button et al, 2022). In addition, conversion from methadone did not appear to influence the success of transition, as all five patients switching from methadone transitioned succesfully.

Regarding the two patients in this study who did not transition successfully, both started the buprenorphine patch, however one later determined they did not wish to take sublingual buprenorphine long-term and the other did not transition to sublingual buprenorphine due to fear

of precipitated withdrawal. Fear of precipitated withdrawal and mistrust of providers are common reasons for both unsuccessful and lengthier induction of buprenorphine among our patients (Button et al., 2022). A facilitator of adherence to buprenorphine therapy is positive experience with the medication. A patient-centered LDBI approach allows patients to have a more positive experience, which is crucial for retention (Teruya, 2014).

Our study differs from other case reports and series, including Buchheit, et al and Weimer, et al, in that the patients described in these reports successfully discontinued full agonist opioids without a taper upon initiation of maintenance buprenorphine (Buchheit et al., 2021; Weimer et al., 2021). This can be appropriate in the setting of chronic pain; however, we have found taper and discontinuation to be challenging in managing acute pain. For instance, 10 out of 19 patients required a prescription for opioid analgesia at discharge due to ongoing pain from their trauma, surgery, or injection-related complication (ie: osteomyelitis). Our patients frequently require extended tapers, regardless of their final buprenorphine dose or their initial MME. Given the fact that buprenorphine should not be expected to cover acute pain needs in addition to their known opioid debt, offering additional opioid analgesia while in the hospital appears reasonable (Courty & Authier, 2012). Abruptly discontinuing opioid analgesia in our patients still experiencing acute pain may cause our patients to opt against initiating buprenorphine in the first place.

This study has several limitations. The small sample size of this pilot study and unbalanced group sizes make comparisons between groups difficult to interpret. This study was conducted in one large academic medical center, limiting the generalizability of the results. For instance, in areas where fentanyl is the predominant opioid, opioid tolerance may be higher and MME prior to transition may be an more important factor in successful transition. The inconsistent documentation of opioid withdrawal symptoms limited our ability to report on withdrawal scores. In addition, patients followed different protocols; the course of the induction patients followed could be influenced by the provider on service, day of week, or admitting unit. Although we had a basic protocol developed, we allowed some flexibility depending on patient preference. Given the relative novelty of LDBI, we often encountered skepticism around the utility of this approach; thus, patients frequently requested slower or delayed inductions and other modifications. This made studying differences and thus developing conclusions more challenging. Lastly, few patients followed an opioid agonist taper throughout the induction, which was often at the discretion of the primary team and could have influenced results.

5. Conclusion

This pilot study examining the success of LDBI via transdermal buprenorphine found high success rates in buprenorphine transition and identified no clear trend towards a correlation with baseline MME requirements or days of transition. Patient-specific adjustments, including lengthening transition time and allowing continuation of full opioid agonists, may be considered in order to effect a high success rate of LDBI.

Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work, and have given their approval for this version to be published

Contributors

All authors contributed to the study conception, design, management, data analysis, and manuscript drafting. ZAK performed data collection.

Declaration of Competing Interest

All authors have nothing to declare.

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