CLINICAL PRACTICE
Clinical Vignettes

Advanced Inpatient Management of Opioid Use Disorder in a Patient Requiring Serial Surgeries

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Opioid use disorder has affected many lives across the US. Medications for opioid use disorder (MOUD), including buprenorphine, have been shown to decrease mortality in this patient population. Here we present a case of a 32-year-old woman on buprenorphine/naloxone undergoing multiple surgical operations, whose course included buprenorphine discontinuation, methadone initiation, and buprenorphine re-induction using a novel "microdosing" approach. This report includes a presentation of the case and a discussion of the clinical decision making and relevant literature to give hospitalbased providers a perspective on management of peri-operative patients on MOUD.

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INTRODUCTION

Opioid use disorder (OUD) has been described by the US surgeon general as a crisis,[1] with over 800,000 Americans reporting recent use of heroin[2] and more than forty-seven thousand deaths resulting from opioid overdose in 2017.[2] One effective treatment involves the use of buprenorphine, a high-affinity, partial agonist at the mu opioid receptor.[3] Studies suggest that buprenorphine—and medications for opioid use disorder (MOUD) more broadly—results in a marked reduction in mortality.[4, 5] Buprenorphine has some benefits over its primary alternative MOUD, methadone, due to its flexibility in prescribing[6] and its respiratory and cardiovascular safety profile.[3] It is commonly prescribed as a combination product with naloxone, which is intended to deter recreational misuse (by IV injection) of the medication.

Unfortunately, buprenorphine's high-affinity and partial agonism at the mu-opioid receptor can render acute and severe pain management more complicated. Other opioids competing for the same receptors may produce less analgesia than desired,[7, 8] and buprenorphine itself can displace other lower affinity opioids at the receptor, potentially resulting in more pain and opioid withdrawal symptoms.[3] These pharmacologic considerations are pertinent in scenarios of peri-operative pain management.

Here we present a case of a 32-year-old woman on buprenorphine/naloxone undergoing multiple surgical operations, whose course included buprenorphine discontinuation, methadone initiation, and buprenorphine re-induction using a novel "micro-dosing" approach.[9, 10] This report includes a presentation of the case and a discussion of the clinical decision making and relevant literature to give hospital-based providers a perspective on management of peri-operative patients on MOUD.

CASE PRESENTATION

Ms. L is a 32-year-old woman with a past medical history of severe OUD in sustained remission on chronic buprenorphine/naloxone maintenance therapy, ADHD, depression, and bipolar disorder. Her opioid use disorder was characterized by a 7-year history of prescription opioid use followed by a 10-year history of IV heroin use. Eventually, she pursued treatment with methadone maintenance therapy, but this was stopped after 6 years due to patient preference. She was then started on buprenorphine/naloxone therapy 2 years prior to admission and had continued on a dose of 16/4 mg daily since that time, resulting in sustained remission.

On the day of admission, she presented to the hospital after a scooter accident in which she sustained a severe right anteromedial foot and ankle degloving injury, as well as partial rupture of her right tibialis anterior tendon and nondisplaced fractures to the first and second metatarsal bones. The patient required emergent wound debridement and synthetic graft placement. Intraoperative evaluation revealed periosteal stripping and severe contamination, resulting in the need for multiple subsequent, painful procedures during her admission. In anticipation of a high analgesic requirement, her buprenorphine/naloxone was discontinued on admission, and she was started on an IV hydromorphone patient-controlled analgesia (PCA) pump at a continuous infusion rate of 0.2 mg per hour, with 0.2 mg demand dose every 10 min. She was then admitted to an internal medicine service for acute pain management due to her history of OUD and partial opioid agonist therapy. Her last dose of buprenorphine/naloxone (16/4 mg daily) was taken the day prior to admission.

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On day 2 of admission, her pain levels increased and the demand dose of the PCA pump was increased to 0.4 mg every 10 min. On day 3 of admission, the patient returned to the operating room for repeat right foot incision and drainage as well as wound vacuum-assisted closure (VAC) placement. The PCA demand dose was continued for acute pain, but the continuous infusion rate was stopped. She subsequently began experiencing a constellation of symptoms including myalgias, anxiety, stomach pain, chills, and restlessness. At this time, an inpatient addiction medicine service was consulted for assistance with management of the patient's discomfort. It was assessed that Ms. L was not experiencing severe post-operative pain, but rather an opioid withdrawal syndrome. Ms. L expressed a desire to receive buprenorphine, but it was thought that this may cause worsening of her withdrawal symptoms and result in inadequate analgesia. As such, she was instead initiated on methadone for her opioid withdrawal at an initial dose of 10 mg followed by 20 mg daily.

On day 4, Ms. L reported resolution of her opioid withdrawal symptoms. The PCA pump was discontinued and she was transitioned to oral hydromorphone 2–4 mg every 3 h as needed, with IV breakthrough as needed. She was continued on the same oral hydromorphone regimen (without need for IV) and methadone on days 4–8 of hospitalization. Ms. L expressed a strong aversion to remaining on methadone long-term, so plans were made to transition her back to buprenorphine upon completion of all surgical procedures via a novel "micro-dosing" approach[9, 10] (see protocol below) that involves administering small, escalating doses of buprenorphine concurrently with other full-agonist opioids.

On day 8, the patient returned to the operating room for a right forearm flap to the right foot. She was subsequently transferred to a surgery service and started back on a hydromorphone PCA pump with a demand dose of 0.4 mg every 10 min and without continuous, basal infusion. Methadone was continued at 20 mg daily to prevent withdrawal symptoms. The PCA pump was continued at the same rate through hospital day 10.

On day 11, she was started on the buprenorphine micro-dosing protocol (Table 1) and transitioned to hydromorphone 2 mg orally every 3 h as needed. The escalation of buprenorphine doses lasted from hospital day 11 to day 17, while the doses of hydromorphone and methadone remained constant. Precipitated withdrawal was not observed, and her pain was well controlled throughout the protocol. Methadone was discontinued on hospital day 17. Her buprenorphine dose remained 4 mg four times daily on hospital day 18, and her buprenorphine dose was increased to 8 mg three times daily on hospital day 19 in preparation for discharge on day 20 on a regimen of buprenorphine/naloxone 8/2 mg three times daily, as well as oral naproxen and acetaminophen for additional pain management. One week after discharge, she was transitioned back to her original dose of buprenorphine 16/4 mg daily by her outpatient provider. She reported no symptoms of withdrawal or increased pain at this dose.

DISCUSSION

Peri-operative pain management can be complex for patients with OUD, particularly if chronically maintained on buprenorphine. Ms. L underwent several changes to her pain regimen based on her clinical course and overall experienced adequate analgesia while also receiving OUD treatment (see Table 4 for a summary of these medications and the estimated morphine milligram equivalents of as-needed full-agonist opioid analgesics required over the hospital stay). Several moments during her course deserve further discussion.

First, upon arrival to the hospital and in the immediate post-operative period, Ms. L's primary team decided not to order buprenorphine. There is currently a lack of consensus and data on continuation of buprenorphine peri-operatively.[11, 12] From a biochemical and anecdotal perspective, patients on high doses of buprenorphine may not receive adequate analgesia from full-agonist opioids due to a lack of available receptors and buprenorphine's high receptor affinity. However, many addiction specialists[7, 13, 14] (including author DT) prefer to maintain patients on buprenorphine—sometimes split three times daily for extra analgesic coverage and at a lower total dose for extra receptor availability—in the peri-operative period due to several reasons. Buprenorphine itself offers signif-

Table 1 Buprenorphine Micro-dosing Protocol

Day of micro-dosing protocol (day of hospitalization)	Buprenorphine* dose	Methadone dose
1 (11)	0.5 mg SL once	20 mg daily
2 (12)	0.5 mg SL BID	20 mg daily
3 (13)	1 mg SL BID	20 mg daily
4 (14)	2 mg SL BID	20 mg daily
5 (15)	4 mg SL BID	20 mg daily
6 (16)	4 mg SL TID	20 mg daily
7 (17)	4 mg SL QID	Discontinued

**Our inpatient pharmacy primarily carries the buprenorphine mono-product (sublingual tablet). However, for doses of 0.5 mg and 1.0 mg, a combination buprenorphine/naloxone product (sublingual film) is used for practical ease of cutting the dose*

Table 2 Opioid Affinity to Mu Opioid Receptor*. Note: Lower K_i indicates higher binding affinity

Full agonist of MOR	Partial agonist of MOR	K_i (nM)
	Buprenorphine	0.22
Hydromorphone		0.37
Morphine		1.17
Fentanyl		1.35
Methadone		3.38
Oxycodone		25.87
Hydrocodone		41.58
Meperidine		450.10
Codeine		734.20

**Abbreviations: MOR, mu opioid receptor; Ki, equilibrium dissociation constant for the test compound; nM, nanomolar concentration*
Adapted from Volpe et al. (2011)[20] and Wang et al. (2007)[21]

Table 3 Plasma Half-lives of Opioid Drugs

Drug	Plasma half-life (h)
Morphine	2–3.5
Hydromorphone	2–3
Oxycodone	2–3
Fentanyl	3.7
Codeine	3
Meperidine	3–4
Methadone	8–59
Buprenorphine	24–42

Adapted from Inturrisi (2002)[22] and FDA package inserts for methadone[23] and buprenorphine[24]

icant and unique analgesic effects *without* a clear "ceiling" effect,[15, 16] some data suggest that full-agonist opioids still have adequate analgesic effect when given in addition to buprenorphine,[16] and the combination of post-operative pain and the need for a re-induction of buprenorphine constitutes a high-risk window for OUD relapse.[17, 18] In Ms. L's case, it may have been optimal to instead continue her buprenorphine/naloxone at the time of admission and to manage her acute severe pain with relatively high doses of full opioid agonists. One study even observed that patients who were not maintained on their MOUDs in the peri-operative period required a longer duration of PCA therapy.[19] If the patient continued to have a poor analgesic response, a dose reduction down to 12 mg of buprenorphine or less[7] could have been considered at that time to allow for additional full agonist opioid activity. Had this been her management course, she may not have experienced opioid withdrawal symptoms necessitating initiation of methadone and a subsequent micro-dosing transition to buprenorphine. Perhaps educating patients on the importance of continuing MAT during surgery would encourage them to advocate for themselves and alert their teams to the importance of suboxone continuation in the peri-operative period.

Second, Ms. L began experiencing withdrawal symptoms post-operatively. It would not have been surprising if her care team attributed her uncomfortable symptoms purely to post-operative pain control and, as a result, prescribed ever-escalating doses of short-acting opioids. However, opioid withdrawal symptoms are best treated by long-acting opioids such as buprenorphine (half-life upwards of 42 h) and methadone (half-life upwards of 59 h), which help to provide a stable, "basal" level of activity at patients' mu-opioid receptors (see Tables 2, 3, and 4). Other adjunctive medications can also be considered for anxiety, restlessness, gastrointestinal upset, and body aches.

Third, Ms. L primarily received hydromorphone as a short acting, acute pain medication. This was decided early in the admission based on hydromorphone's relatively high mu-receptor affinity which could compete with buprenorphine at the receptor. For that reason, fentanyl or morphine would also have been a reasonable choice for short-acting analgesia (see Table 3), although morphine has a wide range of reported affinities and may lack adequate potency unless at very high doses.

Fourth, Ms. L was transitioned back to buprenorphine using a "micro-dosing" approach, modified from a protocol used previously by Terasaki et al.[10] In a recent review documenting many of the different "micro-dosing" strategies used around the world,[25] the authors summarily state, "While there are a variety of micro-induction protocols presented as case series and reports, it is the underlying principle of bridging that makes them effective." Instead of a conventional

Table 4 Summary of Opioid Analgesic Medications Administered During Hospitalization[1]

Hospital day	Oxycodone	Hydromorphone PO	Hydromorphone IV	Oral morphine milligram equivalents[2]	Methadone	Buprenorphine
1	5 mg		0.6 mg	19.5		
2			5.4 mg	108		
3			3 mg	60	10 mg	
4		14 mg	1.6 mg	88	20 mg	
5		24 mg		96	20 mg	
6		24 mg		96	20 mg	
7		24 mg		96	20 mg	
8		12 mg	0.6 mg	36	20 mg	
9			0.2 mg	4	20 mg	
10			0.3 mg	6	20 mg	
11		6 mg	0.1 mg	26	20 mg	0.5 mg
12		8 mg		32	20 mg	1.0 mg
13		10 mg		40	20 mg	2 mg
14		10 mg		40	20 mg	4 mg
15		8 mg		32	20 mg	8 mg
16		10 mg		40	20 mg	12 mg
17		6 mg		24	Discontinued	16 mg
18		2 mg		24		16 mg
19		10 mg		40		24 mg
20 (discharge)						

[1]*All doses indicate the total amount administered over a 24-h period*

[2]*Oral morphine milligram equivalents (MMEs) were calculated for the additive doses of as-needed full-agonist opioid analgesics (oxycodone, oral hydromorphone, and intravenous hydromorphone) given per day. Methadone and buprenorphine were excluded from the MME calculation due to their imprecise conversion to MMEs, the fact that they are partial opioid receptor agonists, and they were given as part of a scheduled regimen rather than as-needed*

buprenorphine induction which involves abrupt cessation of all opioids and the onset of opioid withdrawal symptoms to start, micro-dosing involves very small doses of buprenorphine given concurrently with other opioids in an escalating manner over several days. This minimizes significant displacement of lower affinity opioids and therefore minimizes the risk of precipitated withdrawal. Overall, the absence of the need for abrupt opioid cessation can be especially useful for patients who are medically frail, unwilling to experience withdrawal, at high risk of OUD relapse, or—in the case of Ms. L—continuing to experience post-operative acute pain. This micro-dosing protocol did result in a prolonged hospital length of stay. It can technically be completed as an outpatient, but the logistical and regulatory complexity of concurrent methadone, combined with the need for patient understanding and adherence, adds considerable relapse risk to the patient's care transition. The ultimate goal is to educate providers to continue patients on their buprenorphine peri-operatively, making this situation rare.

In conclusion, it is critical to consider management of acute pain as well as opioid withdrawal symptoms in patients on buprenorphine undergoing surgery, and it is beneficial to have a range of tools—including buprenorphine micro-dosing—widely available for patients with OUD. Access to addiction specialty services and collaboration among various inpatient and outpatient care providers are needed to reduce variability in institutional practice patterns. In addition, more data are needed to guide clinical consensus in this challenging scenario—one that is likely to become more common as growing numbers of patients are treated with MOUD to combat the US opioid crisis.

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Declarations:

Conflict of Interest: *The authors declare that they do not have a conflict of interest.*

REFERENCES

1. US Dept of HHS O of the SG. Facing Addiction in America: the Surgeon General's Spotlight on Opioids. 2018:35. https://addiction.surgeongeneral.gov/sites/default/files/Spotlight-on-Opioids_09192018.pdf.
2. Center for Behavioral Health Statistics and Quality. 2017 National Survey on Drug Use and Health: Detailed Tables. SAMHSA; 2018:2871. https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHDetailedTabs2017/NSDUHDetailedTabs2017.pdf.
3. **Foster B, Twycross R, Mihalyo M, Wilcock A.** Buprenorphine. J Pain Symptom Manag. 2013;45(5):939-949. https://doi.org/10.1016/j.jpainsymman.2013.03.001.
4. **Gibson A, Degenhardt L, Mattick RP, Ali R, White J, O'Brien S.** Exposure to opioid maintenance treatment reduces long-term mortality. Addiction. 2008;103(3):462-468. https://doi.org/10.1111/j.1360-0443.2007.02090.x.
5. **Larochelle MR, Bernson D, Land T, et al.** Medication for opioid use disorder after nonfatal opioid overdose and association with mortality: a cohort study. Ann Intern Med. 2018;169(3):137-145. https://doi.org/10.7326/M17-3107.
6. SAMHSA. Buprenorphine. Published May 31, 2016. https://www.samhsa.gov/medication-assisted-treatment/treatment/buprenorphine.
7. **Lembke A, Ottestad E, Schmiesing C.** Patients maintained on buprenorphine for opioid use disorder should continue buprenorphine through the perioperative period. Pain Med. 2019;20(3):425-428. https://doi.org/10.1093/pm/pny019.
8. **Marie BS, Broglio K.** Managing pain in the setting of opioid use disorder. Pain Manag Nurs. 2020;21(1):26-34. https://doi.org/10.1016/j.pmn.2019.08.003.
9. **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. https://doi.org/10.2147/SAR.S109919.
10. **Terasaki D, Smith C, Calcaterra SL.** Transitioning hospitalized patients with opioid use disorder from methadone to buprenorphine without a period of opioid abstinence using a microdosing protocol. Pharmacotherapy. 2019;39(10):1023-1029. https://doi.org/10.1002/phar.2313.
11. **Thakrar S, Lee J, Martin CE, Iv JB.** Buprenorphine management: a conundrum for the anesthesiologist and beyond - a one-act play. Reg Anesth Pain Med. 2020. https://doi.org/10.1136/rapm-2020-101294.
12. **Edwards DA, Hedrick TL, Jayaram J, et al.** American society for enhanced recovery and perioperative quality initiative joint consensus statement on perioperative management of patients on preoperative opioid therapy. Anesth Analg. 2019;129(2):553–566. https://doi.org/10.1213/ANE.0000000000004018.
13. **Goel A, Azargive S, Weissman JS, et al.** Perioperative Pain and Addiction Interdisciplinary Network (PAIN) clinical practice advisory for perioperative management of buprenorphine: results of a modified Delphi process. Br J Anaesth. 2019;123(2):e333-e342. https://doi.org/10.1016/j.bja.2019.03.044.
14. **Buresh M, Ratner J, Zgierska A, Gordin V, Alvanzo A.** Treating perioperative and acute pain in patients on buprenorphine: narrative literature review and practice recommendations. J Gen Intern Med. 2020. https://doi.org/10.1007/s11606-020-06115-3.
15. **White LD, Hodge A, Vlok R, Hurtado G, Eastern K, Melhuish TM.** The efficacy and adverse effects of buprenorphine in acute pain management: a systematic review and meta-analysis of randomised controlled trials. Br J Anaesth. https://doi.org/10.1016/j.bja.2017.11.086.
16. **Khanna IK, Pillarisetti S.** Buprenorphine - an attractive opioid with underutilized potential in treatment of chronic pain. J Pain Res. 2015;8:859-870. https://doi.org/10.2147/JPR.S85951.
17. **Ward EN, Quaye AN-A, Wilens TE.** Opioid use disorders: perioperative management of a special population. Anesth Analg. 2018;127(2):539-547. https://doi.org/10.1213/ANE.0000000000003477.
18. **Myers J, Compton P.** Addressing the potential for perioperative relapse in those recovering from opioid use disorder. Pain Med. 2018;19(10):1908-1915. https://doi.org/10.1093/pm/pnx277.
19. **Macintyre PE, Russell RA, Usher KAN, Gaughwin M, Huxtable CA.** Pain relief and opioid requirements in the first 24 hours after surgery in patients taking buprenorphine and methadone opioid substitution therapy. Anaesth Intensive Care. 2013;41(2):222-230. https://doi.org/10.1177/0310057X1304100212.
20. **Volpe DA, McMahon Tobin GA, Mellon RD, et al.** Uniform assessment and ranking of opioid μ receptor binding constants for selected opioid drugs. Regul Toxicol Pharmacol. 2011;59(3):385-390. https://doi.org/10.1016/j.yrtph.2010.12.007.
21. **Wang D, Sun X, Sadee W.** Different effects of opioid antagonists on Mu-, Delta-, and Kappa-opioid receptors with and without agonist pretreatment. J Pharmacol Exp Ther. 2007;321(2):544-552. https://doi.org/10.1124/jpet.106.118810.
22. **Inturrisi CE.** Clinical pharmacology of opioids for pain. Clin J Pain. 2002;18(4 Suppl):S3-13. https://doi.org/10.1097/00002508-200207001-00002.
23. Roxane Laboratories, Inc. Dolophine [package insert]. Published online April 2015. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/006134s038lbl.pdf.
24. Indivior, Inc. Suboxone [package insert]. Published online October 2019. https://www.suboxone.com/pdfs/prescribing-information.pdf.
25. **Ghosh SM, Klaire S, Tanguay R, Manek M, Azar P.** A review of novel methods to support the transition from methadone and other full agonist opioids to buprenorphine/naloxone sublingual in both community and acute care settings. Can J Addict. 2019;10(4):41–50. https://doi.org/10.1097/CXA.0000000000000072.