



Open camera or QR reader and scan code to access this article and other resources online.

Top Ten Tips Palliative Care Clinicians Should Know About Buprenorphine

Kyle J. Neale, DO,¹ Melissa B. Weimer, DO, MCR,² Mellar P. Davis, MD,³ Katie Fitzgerald Jones, APRN,⁴ Justin G. Kullgren, PharmD,⁵ Sachin S. Kale, MD,⁶ Julie Childers, MD, MS,⁷ Kathleen Broglio, DPN, APRN,⁸ Jessica S. Merlin, MD, PhD, MBA,⁹ Sarah Peck, MSW,¹⁰ Sheria Y. Francis, MSW,¹¹ Jacqueline Bango, MSW,¹² Christopher A. Jones, MD, MBA,¹³ Zachary Sager, MD,¹⁴ and J. Janet Ho, MD, MPH¹⁵

Abstract

Pain management in palliative care (PC) is becoming more complex as patients survive longer with life-limiting illnesses and population-wide trends involving opioid misuse become more common in serious illness. Buprenorphine, a generally safe partial mu-opioid receptor agonist, has been shown to be effective for both pain management and opioid use disorder. It is critical that PC clinicians become comfortable with indications for its use, strategies for initiation while understanding risks and benefits. This article, written by a team of PC and addiction-trained specialists, including physicians, nurse practitioners, social workers, and a pharmacist, offers 10 tips to demystify buprenorphine use in serious illness.

Keywords: addiction; buprenorphine; opioid use disorder; palliative care

¹The Lois U and Harry R Horvitz Palliative Medicine Program, Department of Palliative Medicine and Supportive Care, Taussig Cancer Institute, Cleveland Clinic, Cleveland, Ohio, USA.

²Program in Addiction Medicine, Department of Medicine, Yale School of Medicine, New Haven, Connecticut, USA.

³Department of Palliative Care, Geisinger Medical Center, Danville, Pennsylvania, USA.

⁴William F. Connell School of Nursing, Boston College, Chestnut Hill, Massachusetts, USA.

⁵Palliative Medicine Clinical Pharmacy, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA.

⁶Division of Palliative Medicine, Department of Medicine, The Ohio State University Wexner Medical Center, Columbus, Ohio, USA.

⁷Section of Palliative Care and Medical Ethics, Division of General Internal Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA.

⁸Section of Palliative Medicine, Geisel School of Medicine at Dartmouth, Collaboratory for Implementation Sciences at Dartmouth, Lebanon, New Hampshire, USA.

⁹Section of Palliative Care and Medical Ethics and Palliative Research Center, Division of General Internal Medicine, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA.

¹⁰Division of Palliative Medicine, Emory University Healthcare Midtown, Atlanta, Georgia, USA.

¹¹Collaborative Care Management, University of Pittsburgh Medical Center Presbyterian Shadyside, Pittsburgh, Pennsylvania, USA.

¹²The Juniper Center, Chicago, Illinois, USA.

¹³Department of Medicine, Duke University School of Medicine, Durham, North Carolina, USA.

¹⁴Department of Psychosocial Oncology and Palliative Care, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA.

¹⁵Division of Palliative Medicine, University of California San Francisco, San Francisco, California, USA.

Accepted August 2, 2022.

Introduction

THE MANAGEMENT OF PAIN in patients with serious illness is an integral part of palliative care (PC). Opioids are a cornerstone of therapy but several historical factors have recently led to prescribing concerns. The opioid overdose epidemic continues to kill tens of thousands of Americans, having increased sixfold since 1999.¹ The cancer survivorship cohort is growing nationally with over one third having attendant chronic pain.² PC has moved “upstream” earlier in disease courses leading to more patient encounters and potentially long-term opioid prescribing.³

Long-term opioid therapy is associated with myriad risks, including sleep disordered breathing, tolerance, opioid dependence, dysphoria, allodynia, hyperalgesia, and the development of opioid use disorder (OUD).⁴ Opioid tolerance and dependence, physiologic adaptations that occur from chronic opioid use, are a reality of opioid treatment; however, the risk of developing OUD may also be as high as 10% for some patients over 10 years of prescribed opioid therapy for nonmalignant pain.⁵ There is substantial evidence that long-term opioid therapy, especially in combination with benzodiazepines, gabapentinoids, and other sedative hypnotics, is associated with increased mortality.⁶

In addition to these potential opioid-related harms, PC clinicians are encountering more people with preexisting OUD.^{7,8} A recent systematic review found the prevalence of OUDs among individuals with cancer to be ~8%.⁹ These individuals are more likely to develop chronic, life-threatening conditions with a high symptom burden that need palliative support.¹⁰

It is therefore surprising that as recently as 2015, one study reported that half of ambulatory palliative clinics felt opioid misuse, the use of nonprescribed opioids or use differently than prescribed, was a concern for their practice.¹¹ This likely reflects low confidence among palliative clinicians in assessing and treating opioid misuse and comorbid chronic pain.^{12,13}

Buprenorphine offers a potential way forward. It is a synthetic opioid that provides effective analgesia with a favorable adverse effect profile and has many advantages over full agonist opioids when treating patients with comorbid pain and opioid misuse or OUD. Despite these benefits, buprenorphine is underutilized.¹⁴ This article aims to demystify buprenorphine and empower clinicians to use this medicine to safely and effectively treat both pain and OUD.

Tip 1: Buprenorphine Is an Opioid with Unique Pharmacology and Fewer Adverse Side Effects Compared to Full Agonist Opioids

Buprenorphine is a Schedule III partial opioid agonist initially developed as an analgesic and later as a treatment for OUD.^{15,16} Buprenorphine has a high affinity for and slow dissociation from the mu-opioid receptor (MOR).¹⁷ The labeling of buprenorphine as a “partial” opioid agonist is based on a comparison of MOR G-protein activation to other potent opioid agonists in *in vitro* studies.¹⁵ This “partial” agonism refers only to G-protein activation; it should not be clinically equated to partial analgesia.¹⁸ Buprenorphine is a 6-transmembrane MOR agonist that induces phosphorylation of specific opioid G-protein subunits without significantly recruiting beta-arrestin proteins. The lack of beta-arrestin activity causes less receptor internalization and down-

regulation of the MOR. These pharmacodynamics may explain how it provides analgesia with a more favorable opioid adverse effect profile, including less withdrawal, less tolerance, and a ceiling effect on respiratory depression.^{19–23}

Buprenorphine has been reported to have full agonism at the opioid receptor-like 1 (ORL-1), but interactions only occur with doses higher than may be achieved clinically.²⁴ Buprenorphine is a kappa receptor antagonist, which accounts for its antidepressant activity and blunted opioid craving.^{15,25–29} Antagonist activity at the kappa and delta-opioid receptors appears to lessen misuse, sedation, and dysphoria.³⁰ In addition, kappa antagonism may result in improved stability of comorbid mental health conditions such as anxiety and depression.^{30,31}

Tip 2: Buprenorphine Can Be an Effective Analgesic and May Be the Preferred Initial Opioid Analgesic in Selected Patient Populations

The Department of Health and Human Services encourages that buprenorphine be considered before scheduled II opioids (e.g., oxycodone, morphine) in the management of chronic pain.³² Analgesic efficacy is equivalent if not greater than oxycodone, fentanyl, hydromorphone, hydrocodone, and morphine.^{33–39} Individuals on high-dose schedule II opioids who are unable to taper due to worsening pain and/or function, sometimes referred to as complex persistent opioid dependence, may benefit from buprenorphine.^{40–42} The unique pharmacology of buprenorphine allows analgesia with reduced risk of respiratory depression and misuse liability relative to oxycodone, morphine, and fentanyl and hence is the analgesic of choice for someone with pain and at risk for OUD (Tip 5).^{43,44}

Buprenorphine pharmacokinetics are unchanged in older adults.⁴⁵ Buprenorphine causes less hypogonadism in men compared with methadone and is less immunosuppressive than fentanyl or morphine.^{46,47} Immunosuppression with opioids is becoming an important issue in patients on checkpoint inhibitors for their cancer therapy.⁴⁸ Although buprenorphine is associated with prolongation of the QTc interval, it does not interfere with human Ether-à-go-go-Related Gene (hERG) nor L-type calcium channels and has not been associated with Torsades de Pointes. Consequently, it does not require electrocardiogram (EKG) monitoring, unlike methadone, and is safe in heart failure and in individuals with prolonged QTc.⁴⁹

Buprenorphine has antidepressant activity but does not block monoamine reuptake and hence is safe to use in those on antidepressants without a risk for precipitating a serotonin syndrome.^{50,51} Buprenorphine pharmacokinetics are unchanged in renal failure and it is a relatively safe opioid to use in hepatic failure.^{18,28,52} Buprenorphine has a long-acting sublingual (SL) or buccal formulation making it a favorable choice when patients cannot swallow.¹⁸

Tip 3: Multiple Buprenorphine Formulations Are Available for the Treatment of Pain and/or OUD; Product Selection Is Determined by Several Factors Including Opioid Tolerance, Clinical Indication, Patient Preference, Insurance Factors, and Exposure to a Full Agonist

Buprenorphine is available in multiple formulations and is FDA approved for either chronic pain or OUD.²⁰ Table 1

TABLE 1. BUPRENORPHINE FORMULATIONS

Name	Route	Dose range	FDA indication	Off label indication	Considerations
Low-dose buprenorphine products ^a					
Butrans [®]	TD patch	Dose range 5–20 µg/hour every seven days	Chronic pain	Low-dose initiation for treatment of OUD	Low to moderate doses can be initiated in persons who are opioid naïve
Belbuca [®]	Transmucosal film	Dose range 75–900 µg every 12 hours	Chronic pain	Low-dose initiation for treatment of OUD	Low to moderate doses can be initiated in persons who are opioid naïve
Buprenex [®]	IV or intramuscular	300 µg IM/IV q6–eight hours PRN	Acute moderate—severe pain	Low-dose initiation for treatment of OUD	Can be used in opioid tolerant or naïve persons
Moderate-high-dose buprenorphine products ^b					
Suboxone [®] Zubsolv [®]	SL transmucosal	Available products from 2 mg buprenorphine /0.5 naloxone to 12 mg buprenorphine/3 mg naloxone	OUD	Chronic pain	Buprenorphine dose for OUD is typically 12–24 mg/daily For pain give in split doses (every 6, 8 or 12 hours)
Subutex [®]	SL transmucosal	Buprenorphine 2–8 mg	OUD	Chronic pain	Dose for OUD is typically 12–24 mg/daily Limited to use in pregnancy, naloxone allergy, or end-stage liver disease

^aA diagnosis of pain is required to prescribe low-dose buprenorphine formulations outside of the hospital.

^bDEA X waiver required for OUD indication.

IV, intravenous; OUD, opioid use disorder; SL, sublingual; TD, transdermal.

Source: Jones,¹⁶ Hickey et al,²⁰ Degan and Mousa,⁵⁷ Cohen et al,⁶⁰ Gudim and Fudin.⁶¹

provides a comprehensive overview of potency, route, and relevant considerations. Low-dose buprenorphine products in micrograms, including transdermal (Butrans[®]) or buccal (Belbuca[®]), are FDA approved for chronic pain but have been described for use during low-dose buprenorphine initiations (see Tip 6).^{35,38,53} Moderate to high-dose transmucosal or SL buprenorphine is available as a mono-product (Subutex[®]) or in combination with naloxone (Suboxone[®], Zubsolv[®]).²⁰ Naloxone coformulation minimizes the risk for tampering as it becomes active if injected, although no formulation of buprenorphine is resistant to misuse.⁵⁴

Importantly, moderate- to high-dose buprenorphine products can be used off-label for chronic pain in people who are opioid-tolerant.^{15,55} These products are typically dosed once daily for OUD treatment, but the total dose can be divided, as frequently as every six hours, to optimize analgesia.^{16,56,57} The mono-product buprenorphine (Subutex) for treatment of OUD is limited to use in pregnant individuals, those with a naloxone allergy, or with end-stage liver disease when naloxone may have increased bioavailability; these limitations do not exist when used off label for the treatment of chronic pain.⁵⁸ Notably, treating pain with high-dose buprenorphine products off-label, without use of an X-waiver, may be subject to increased scrutiny by insurers, institutions, and pharmacies; therefore, all clinicians are encouraged to obtain an X-waiver (see Tip 4).^{31,55,59}

Tip 4: Buprenorphine Is a Highly Effective, First-Line Medical Therapy for Treatment of OUD

Moderate to high-dose buprenorphine is a lifesaving treatment for individuals with OUD.⁶² Buprenorphine treats opioid withdrawal, reduces opioid cravings, reduces opioid use, reduces all cause and overdose-related mortality, and promotes patient recovery.⁶³ Therapeutically dosed buprenorphine is as effective as methadone for these outcomes.⁶⁴ Its use improves patient retention in OUD treatment compared to placebo.⁶⁵ Buprenorphine is associated with a 37% reduction of all-cause mortality after overdose.⁶⁶

Despite these benefits, buprenorphine regulations have frustratingly limited its utilization.⁶⁷ These regulations recently became less onerous. In April 2021, the Department of Health and Human Services exempted eligible physicians and advanced practice providers from training requirements to obtain the X-waiver license to treat up to 30 patients with buprenorphine for OUD.⁶⁸ The X-waiver application now takes approximately five minutes and waivers are typically granted in one to two weeks. Training is encouraged but no longer mandatory except in certain states.⁶⁹

Buprenorphine initiation can be safely done in the office or at home with appropriate patient education and telephone support.⁶⁸ Home-based buprenorphine initiations are

increasingly common given logistical challenges in the office setting and patient-preference. In some states, buprenorphine treatment can now be offered by telehealth given regulatory changes related to COVID-19.^{69,70} Buprenorphine treatment in combination with counseling can be more effective for some patients; however, buprenorphine should not be withheld from patients who do not wish to engage in counseling unless required by state regulations.⁷¹

Tip 5: Buprenorphine Has Less Risk of Opioid Overdose Compared to Full Agonist Opioids and Can Be a Useful Harm Reduction Tool

Several factors make buprenorphine a safer opioid for seriously ill individuals with an OUD. Buprenorphine has a ceiling effect on respiratory depression and its pharmacokinetics are not altered by renal impairment or advanced age.⁷² Overdose deaths involving buprenorphine alone are rare and buprenorphine may even reduce the risk of overdose in individuals who continue to use nonprescribed opioids.^{73,74} While overdoses with buprenorphine can occur, as with accidental ingestion by children or when combined with respiratory depressants, it remains a useful harm reduction tool and a life-saving intervention for patients with OUD. Overall, buprenorphine use reduces all-cause mortality in individuals who use drugs.⁷⁵

As with any chronic disease treatment, some individuals taking buprenorphine for OUD continue to show signs of active disease. If a patient prescribed buprenorphine continues to use other nonprescribed opioids, providers should consider increasing other supports and buprenorphine treatment doses. In addition, many individuals with OUD use nonopioid substances such as stimulants or anxiolytics. In cases where the use of nonprescribed substances is problematic, buprenorphine should be continued while the clinician uses strategies such as motivational enhancement or referral to peer support groups to develop meaningful, patient-centered therapeutic goals that may or may not include abstinence.⁷¹

Examples of other substance use goals may include using less often, in a less risky manner (obtaining clean needles or not using alone), or achieving other life goals possibly affected by substance use. These examples are collectively called harm reduction and are an evidence-based strategy to keep people who use drugs alive and as healthy as possible.⁷⁶

Tip 6: There Are Several Methods to Initiate Buprenorphine Therapy, Depending on Clinical Circumstances and Available Formulary

Moderate dose initiation (aka traditional approach)

Traditional initiation requires the patient to stop use of all full opioid agonists (8–12 hours for short-acting, 24 hours for long-acting, and at least 36 hours for methadone) and enter mild to moderate opioid withdrawal (clinical opioid withdrawal scale >8). Once achieved, buprenorphine is administered at 2–4 mg SL increments every one to two hours until withdrawal is relieved (maximum dose of 8 mg on day 1).^{77,78} Buprenorphine is then titrated by 2–4 mg SL every two hours as needed to achieve effects for pain or OUD over the next few days (day 2 max 16 mg SL).

Further adjustments typically occur after steady state is reached in three to seven days (therapeutic goal in OUD is 16–24 mg SL).

In PC, this initiation method may be most appropriate for patients who are already presenting in a degree of opioid withdrawal.⁷⁹ Medications that treat distressing withdrawal symptoms—clonidine for noradrenergic hyperactivity, ibuprofen for muscle cramps, trazodone for insomnia, ondansetron for nausea, and loperamide for loose stools—should be used liberally as needed.

Low-dose initiation (aka Bernese method; microinduction)

For opioid tolerant patients, low-dose buprenorphine initiation involves continuing full agonist opioids while concurrently adding small doses of buprenorphine (typically <2 mg SL) over time with gradual increases in both the dose and frequency of buprenorphine until a threshold therapeutic dose is achieved.²³ This dosing strategy allows the buprenorphine to gradually occupy MORs in a way that minimizes the risk of precipitated withdrawal. The full agonist opioids are continued until a therapeutic dose of buprenorphine is reached, at which time they are stopped or tapered off.^{4,80–82}

Low-dose initiation protocols have been described in both inpatient and outpatient settings and typically take place over 3–14 days depending on the setting (faster initiations are possible inpatient), clinical scenario, patient housing stability, and patient comfort with following multi-step instructions.⁸³ Initiation protocols can be slowed or paused at any step if a patient experiences discomfort or lengthened for patients on high doses long-acting full MOR agonists such as methadone. Table 2 describes a variety of published protocols.

There are no published randomized trials to inform guidelines around low-dose initiation to date. Reassuringly, a number of case reports/series convincingly support the safety and tolerability of this approach.^{4,84} Care should be taken regarding the speed of buprenorphine titration as well as whether and when to taper full agonist, usually when buprenorphine has reached 8–12 mg with comorbid pain and OUD versus 6 mg SL/day for pain only. When in doubt, reaching out to peers, mentors with experience, or colleagues in pain management or addiction care can be invaluable.

We recommend the low-dose approach for patients maintained on full MOR agonists, patients in the postoperative setting receiving full MOR agonists, patients with use of nonpharmaceutical fentanyl intravenous (IV), and patients who may have experienced or have a significant fear of precipitated withdrawal in the past.

Tip 7: Published Equianalgesic Conversions for Buprenorphine Formulations Are Not Reliable

Buprenorphine's unique pharmacokinetic and pharmacodynamic profile make comparisons to other opioids challenging given variability in published morphine equivalents with conversion factors ranging from 10 to 110. Buprenorphine no longer has a morphine milligram equivalents (MME) factor with the Centers for Disease Control as there is not the same dose-dependent overdose risk as seen with schedule II opioids.⁸⁹

TABLE 2. LOW-DOSE INITIATION PROTOCOLS USING DIFFERENT BUPRENORPHINE FORMULATIONS

Formulation	TD ^{a,85}	TD ^{b,85}	Buccal film ^{c,86}	SL tab/ film ^{d,87}	SL tab/ film ^{e,55}	IV ^{f,88}
Day 1	20 µg/hour TD— first patch	20 µg/hour TD	225 µg PO (75 + 150 µg film) once	0.5 mg SL ^g once	0.5 mg SL BID	0.15 mg IV Q6 hour
Day 2	20 µg/hour TD— second patch	1 mg SL BID	225 µg PO BID	0.5 mg SL BID	1 mg SL BID	0.3 mg IV Q6 hour
Day 3	1 mg SL once	1 mg SL TID	450 µg PO BID	1 mg SL BID	1 mg SL TID	0.6 mg IV Q6 hour
Day 4	1 mg SL BID	2 mg SL TID	2 mg SL BID	2 mg SL BID	2 mg SL TID ^g	4 mg SL Q6 hour
Day 5	2 mg SL BID	4 mg SL TID ^g	4 mg SL BID	3 mg SL BID	4 mg SL TID	8 mg SL BID ^g
Day 6	3 mg SL BID		4 mg SL TID	4 mg SL BID		
Day 7	4 mg SL BID		4 mg SL TID to 8 mg SL BID ^g	12 mg SL ^g		
Day 8	5 mg SL BID					
Day 9	6 mg SL BID					
Day 10	8 mg SL BID ^g					
Cost	\$§		\$\$\$	\$		\$\$\$\$

Full agonist opioids are continued at the current dose until indicated.

^aRemove TD patches as they expire in seven days and do not replace. TD patches should be written for FDA approved indication of “pain” only in the outpatient setting; any opioids can be used to treat withdrawal or OUD inpatient. Protocol in patients on high-dose methadone (80 mg daily).

^bRemove TD patches as they expire in seven days and do not replace. Protocol in patient with concurrent acute pain. Full agonists were tapered starting on day 5.

^cBuccal films in the outpatient setting can only be written for “pain”; inpatient settings can use any opioid to treat OUD or opioid withdrawal.

^d0.5 mg SL buprenorphine or buprenorphine-naloxone dose is achieved by cutting a 2 mg film into quarters. Protocol in patients with OUD.

^e0.5 mg SL dose achieved by cutting 2 mg film or tablet into quarters. Protocol in patients with chronic pain, without OUD.

^f0.15 mg IV is roughly equivalent to 0.5 mg SL. Protocol details a rapid initiation from full agonist in an inpatient setting.

^gDay on which full agonist was stopped or tapered. In most protocols, buprenorphine dose was further adjusted to symptoms by 4–8 mg SL daily.

BID, twice daily; PO, per oral; TID, three times daily.

The original data used to develop a conversion factor came from a postsurgical pain study comparing intramuscular (IM) morphine to a version of SL buprenorphine no longer commercially available and with pharmacokinetics distinct from presently available options.^{90,91} In addition, several studies comparing IV/IM buprenorphine to IM morphine had variable dosing strategies and measured outcomes, adding to the difficulty determining a consistent equianalgesic conversion factor.^{92,93}

Other official guidance contradicts published evidence. The manufacturers of two buprenorphine formulations approved for pain, transdermal patch, and buccal film recommend a reduction or complete taper from other opioids when rotating to buprenorphine, which may no longer be necessary given new low-dose initiation strategies (Tip 6).⁹⁴ We advise clinicians to follow one of the described low-dose initiation strategies and titrate buprenorphine based on patient-reported withdrawal symptoms, indication (OUD or

pain), and general sense of opioid tolerance (e.g., only low-dose products are recommended for opioid naive patients), rather than focusing on anticipated MME.

Multiple buprenorphine formulations are available (Tip 3). Table 3 accounts for their different bioavailabilities and offers approximate equivalencies.

Tip 8: Buprenorphine Therapy Should Be Continued for Acute Pain or in the Perioperative Period

Uncertainty on managing buprenorphine during acute pain episodes exists due to its unique pharmacology as well as mixed historical recommendations based largely on case reports.^{95–98} These patients are at increased risk for poor pain control given higher relative opioid need and clinician opiophobia.^{20,99} Achieving pain control is paramount due to risks of poorly controlled postoperative pain evolving into chronic pain, as pain is a primary risk factor for relapse in OUD.^{100–102}

TABLE 3. APPROXIMATE EQUIVALENCIES BETWEEN VARIOUS BUPRENORPHINE FORMULATIONS

Formulation	TD ^a	Buccal	SL	IV
Bioavailability	~ 15%	46%–65%	~ 30%	100%
Equivalency	7.5 µg/hour	225 µg	0.5 mg	150 µg

^aThe TD patch delivers a much higher concentration to the skin to account for reduced bioavailability. Thus, the patch strength represents systemic effect, not merely what is delivered to the skin.

Source: Hickey et al.²⁰

Current evidence no longer recommends discontinuing buprenorphine when treating acute pain.¹⁰³ Stopping buprenorphine contributes to logistical challenges, potentiating prolonged lengths of stay, while also increasing the risk for patient harm, including precipitated withdrawal, worse pain, and respiratory depression due to overcompensating for opioid debt with a full MOR agonist.¹⁰⁴ In addition, discontinuing buprenorphine is often unnecessary as sufficient MORs are available even at doses of 16 mg SL buprenorphine per day.¹⁰⁵ In summary, full agonist opioids are effective when treating acute pain in patients on buprenorphine for chronic pain or OUD.^{106–112}

A consensus guideline by a working group representing pain management, addiction medicine, and pharmacy health services on buprenorphine management during the perioperative period as well as expert reviews on management during acute pain include the following recommendations^{18,21,113–115}:

- Utilize multimodal analgesia by maximizing nonopioid adjuvants, including ketamine, and consider regional or neuraxial blocks for moderate-severe pain.
- Continue buprenorphine. If prescribed for OUD, then consider dividing doses and/or increasing dose. For chronic pain, consider temporarily reducing buprenorphine dose, as tolerated, to 12–16 mg SL per day to increase bioavailability of MOR if full opioid agonists are indicated, although this is not required in all patients.
- For uncontrolled pain despite maximizing adjuvant analgesics, use full agonist immediate release opioids with competitive binding at the MOR (hydromorphone, fentanyl) at higher doses as needed.
- Continue buprenorphine on discharge. If prescribing additional full opioid agonists, coordinate plan with outpatient clinician.

Tip 9: All Health Care Workers Should Be Prepared to Actively Dispel Misconceptions and Stigma Related to Buprenorphine Use

The following are evidence-based statements to counteract common misconceptions about buprenorphine.

- Buprenorphine does not replace one “addiction” for another.¹¹⁶ OUD is underscored by the compulsive use of an opioid despite negative consequences on the individual’s life. Buprenorphine is medication treatment for OUD that reduces cravings for other opioids, provides stability from the craving-withdrawal cycle, and helps patients reduce the risk of negative consequences of compulsive use.
- Newer low-dose buprenorphine initiation strategies limit the risk of significant withdrawal and pain. Patients who have tried nonprescribed buprenorphine may have experienced severe withdrawal if there was still a full agonist opioid in their system. Newer transition strategies minimize precipitated withdrawal potential (Tip 6).¹¹⁷ In addition, the naloxone component is inactive except in severe hepatic impairment and does not cause withdrawal when taken as prescribed.
- Buprenorphine can effectively treat pain. Patients may believe that buprenorphine only treats OUD. There is

overwhelming evidence supporting its use as an analgesic (Tip 2) in addition to its efficacy treating OUD. Also, buprenorphine does not block analgesic effects of additional full opioid agonists.

- Prescribing buprenorphine for OUD is within the realm of PC specialists. The “X Waiver” was created to expand treatment access beyond specialty care. In fact, the intent was to promote treatment by primary care. PC specialists possess skills that significantly overlap with primary addiction medicine and equip clinicians to treat concurrent OUD in patients with serious illness (Tip 10).
- Patients prescribed buprenorphine for OUD may still require additional opioids for pain. Prescribing additional opioids needs to be context specific and with appropriate safeguards. A blanket refusal to prescribe additional opioids risks undertreating pain in this vulnerable population, possibly leading to relapse and/or worse suffering.

Tip 10: Prescribing Buprenorphine to Treat OUD in Individuals with Serious Illness Is Essential to the Practice of PC Because It Addresses Suffering

Suffering, as defined by Eric Cassell, is “the state of severe distress associated with events that threaten the intactness of the person,” and “extends beyond the physical.”¹¹⁸ The suffering associated with active OUD includes cycles of withdrawal and craving, reduced quality of life, and difficulty maintaining important personal relationships, among other challenges. PC teams are well-suited to address OUD-related suffering and stigma because of our interdisciplinary team approach.¹¹⁹ Palliative teams may alleviate physical suffering by treating craving, withdrawal, and pain with buprenorphine accompanied by psychosocial support. All members of the team can address the social-emotional, existential, trauma-based suffering that often accompanies addiction.

Indeed, the palliative social worker might address feelings of destabilization after losing employment and/or safe housing, thereby allowing the patient to attend to treatment of withdrawal and cravings. The PC chaplain can be instrumental in providing support for spiritual distress and acceptance of medication treatment that can be traditionally stigmatized by peer support organizations such as alcoholic anonymous.

Conclusion

Buprenorphine is an opioid that provides effective analgesia for patients with pain and serious illness, has a low adverse effect profile, and can be life saving for patients suffering from OUD. It should be an essential treatment for all palliative clinicians to understand and utilize.

Funding Information

No funding was received for this article.

Author Disclosure Statement

No competing financial interests exist.

References

1. National Institute on Drug Abuse. Overdose Death Rates. Bethesda, MD; 2022. Available from: <https://nida.nih.gov/drug-topics/trends-statistics/overdose-death-rates> [Last accessed: July 25, 2022].
2. Jiang C, Wang H, Wang Q, et al. Prevalence of chronic pain and high-impact chronic pain in cancer survivors in the United States. *JAMA Oncol* 2019;5(8):1224–1226; doi: 10.1001/jamaoncol.2019.1439
3. Rabow M, Kvale E, Barbour L, et al. Moving upstream: A review of the evidence of the impact of outpatient palliative care. *J Palliat Med* 2013;16(12):1540–1549; doi: 10.1089/jpm.2013.0153
4. Quirk K, Stevenson M. Buprenorphine microdosing for the pain and palliative care clinician. *J Palliat Med* 2022; 25(1):145–154; doi: 10.1089/jpm.2021.0378
5. Vowles KE, McEntee ML, Julnes PS, et al. Rates of opioid misuse, abuse, and addiction in chronic pain: A systematic review and data synthesis. *Pain* 2015;156(4): 569–576; doi: 10.1097/01.j.pain.0000460357.01998.f1
6. Merlin JS, Young SR, Arnold R, et al. Managing opioids, including misuse and addiction, in patients with serious illness in ambulatory palliative care: A qualitative study. *Am J Hosp Palliat Care* 2020;37(7):507–513; doi: 10.1177/1049909119890556
7. Wen H, Borders TF, Cummings JR. Trends in buprenorphine prescribing by physician specialty. *Health Aff (Millwood)* 2019;38(1):24–28; doi: 10.1377/hlthaff.2018.05145
8. 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. *Drug Alcohol Depend* 2020;213:108083; doi: 10.1016/j.drugalcdep.2020.108083
9. Preux C, Bertin M, Tarot A, et al. Prevalence of opioid use disorder among patients with cancer-related pain: A systematic review. *J Clin Med* 2022;11(6):1594; doi: 10.3390/jcm11061594
10. Ebenau A, Dijkstra B, Ter Huurne C, et al. Palliative care for people with substance use disorder and multiple problems: A qualitative study on experiences of patients and proxies. *BMC Palliat Care* 2019;18(1):56; doi: 10.1186/s12904-019-0443-4
11. Tan PD, Barclay JS, Blackhall LJ. Do palliative care clinics screen for substance abuse and diversion? Results of a national survey. *J Palliat Med* 2015;18(9):752–757; doi: 10.1089/jpm.2015.0098
12. Childers JW, Arnold RM. “I feel uncomfortable ‘calling a patient out’”: Educational needs of palliative medicine fellows in managing opioid misuse. *J Pain Symptom Manage*. 2012;43(2):253–260; doi: 10.1016/j.jpainsymman.2011.03.009
13. Janet Ho J, Jones KF, Sager Z, et al. Barriers to buprenorphine prescribing for opioid use disorder in hospice and palliative care. *J Pain Symptom Manage* 2022;64(2): 119–127; doi: 10.1016/j.jpainsymman.2022.05.004
14. Khanna IK, Pillarisetti S. Buprenorphine—An attractive opioid with underutilized potential in treatment of chronic pain. *J Pain Res* 2015;8:859–870; doi: 10.2147/JPR.S85951
15. Webster L, Gudin J, Raffa RB, et al. Understanding buprenorphine for use in chronic pain: Expert opinion. *Pain Med* 2020;21(4):714–723; doi: 10.1093/pm/pnz356
16. Jones KF. Buprenorphine use in palliative care. *J Hosp Palliat Nurs* 2019;21(6):540–547; doi: 10.1097/NJH.0000000000000598
17. Ahn JS, Lin J, Ogawa S, et al. Transdermal buprenorphine and fentanyl patches in cancer pain: A network systematic review. *J Pain Res* 2017;10:1963–1972; doi: 10.2147/JPR.S140320
18. Davis MP. Twelve reasons for considering buprenorphine as a frontline analgesic in the management of pain. *J Support Oncol* 2012;10(6):209–219; doi: 10.1016/j.suponc.2012.05.002
19. Davis MP, Pasternak G, Behm B. Treating chronic pain: An overview of clinical studies centered on the buprenorphine option. *Drugs* 2018;78(12):1211–1228; doi: 10.1007/s40265-018-0953-z
20. Hickey T, Abelleira A, Acampora G, et al. Perioperative buprenorphine management: A multidisciplinary approach. *Med Clin North Am* 2022;106(1):169–185; doi: 10.1016/j.mcna.2021.09.001
21. Golčić M, Dobrila-Dintinjana R, Golčić G, et al. Differences between transdermal fentanyl and buprenorphine in the elderly hospice patients. *Pain Res Treat* 2018;2018: 8610538; doi: 10.1155/2018/8610538
22. Grinnell SG, Ansonoff M, Marrone GF, et al. Mediation of buprenorphine analgesia by a combination of traditional and truncated mu opioid receptor splice variants. *Synapse* 2016;70(10):395–407; doi: 10.1002/syn.21914
23. De Aquino JP, Parida S, Sofuoglu M. The pharmacology of buprenorphine microinduction for opioid use disorder. *Clin Drug Investig* 2021;41(5):425–436; doi: 10.1007/s40261-021-01032-7
24. Spagnolo B, Calo G, Polgar WE, et al. Activities of mixed NOP and mu-opioid receptor ligands. *Br J Pharmacol* 2008;153(3):609–619; doi: 10.1038/sj.bjp.0707598
25. Browne CA, Lucki I. Targeting opioid dysregulation in depression for the development of novel therapeutics. *Pharmacol Ther* 2019;201:51–76; doi: 10.1016/j.pharmthera.2019.04.009
26. Burke NN, Li Y, Deaver DR, et al. Chronic administration of buprenorphine in combination with samidorphan produces sustained effects in olfactory bulbectomized rats and Wistar-Kyoto rats. *J Psychopharmacol* 2019;33(12): 1620–1627; doi: 10.1177/0269881119872203
27. Günther T, Dasgupta P, Mann A, et al. Targeting multiple opioid receptors—Improved analgesics with reduced side effects? *Br J Pharmacol* 2018;175(14):2857–2868; doi: 10.1111/bph.13809
28. Lutfy K, Cowan A. Buprenorphine: A unique drug with complex pharmacology. *Curr Neuropharmacol* 2004;2(4): 395–402; doi: 10.2174/1570159043359477
29. Falcon E, Browne CA, Leon RM, et al. Antidepressant-like effects of buprenorphine are mediated by kappa opioid receptors. *Neuropsychopharmacology* 2016;41(9): 2344–2351; doi: 10.1038/npp.2016.38
30. Fava M, Thase ME, Trivedi MH, et al. Opioid system modulation with buprenorphine/samidorphan combination for major depressive disorder: Two randomized controlled studies. *Mol Psychiatry*. 2020;25(7):1580–1591; doi: 10.1038/s41380-018-0284-1
31. Jones KF, Merlin JS. Approaches to opioid prescribing in cancer survivors: Lessons learned from the general literature. *Cancer* 2022;128(3):449–455; doi: 10.1002/cncr.33961
32. US Department of Health and Human Services. Pain Management Best Practices Inter-Agency Task Force

- Report: Updates, Gaps, Inconsistencies, and Recommendations. 2019. Available from: <https://www.hhs.gov/sites/default/files/pain-mgmt-best-practices-draft-final-report-05062019.pdf> [Last accessed: July 25, 2022].
33. Gimbel J, Spierings ELH, Katz N, et al. Efficacy and tolerability of buccal buprenorphine in opioid-experienced patients with moderate to severe chronic low back pain: Results of a phase 3, enriched enrollment, randomized withdrawal study. *Pain* 2016;157(11):2517–2526; doi: 10.1097/j.pain.0000000000000670
 34. Hale M, Garofoli M, Raffa RB. Benefit-risk analysis of buprenorphine for pain management. *J Pain Res* 2021;14:1359–1369; doi: 10.2147/JPR.S305146
 35. Hale M, Gimbel J, Rauck R. Buprenorphine buccal film for chronic pain management. *Pain Manag* 2020;10(4):213–223; doi: 10.2217/pmt-2020-0013
 36. Hale M, Urdaneta V, Kirby MT, et al. Long-term safety and analgesic efficacy of buprenorphine buccal film in patients with moderate-to-severe chronic pain requiring around-the-clock opioids. *J Pain Res* 2017;10:233–240; doi: 10.2147/JPR.S120170
 37. Steiner D, Munera C, Hale M, et al. Efficacy and safety of buprenorphine transdermal system (BTDS) for chronic moderate to severe low back pain: A randomized, double-blind study. *J Pain* 2011;12(11):1163–1173; doi: 10.1016/j.jpain.2011.06.003
 38. Rauck RL, Potts J, Xiang Q, et al. Efficacy and tolerability of buccal buprenorphine in opioid-naïve patients with moderate to severe chronic low back pain. *Postgrad Med* 2016;128(1):1–11; doi: 10.1080/00325481.2016.1128307
 39. Pergolizzi JV, Jr., Magnusson P, LeQuang JA, et al. Transdermal buprenorphine for acute pain in the clinical setting: A narrative review. *J Pain Res* 2021;14:871–879; doi: 10.2147/JPR.S280572
 40. Manhapra A, Sullivan MD, Ballantyne JC, et al. Complex persistent opioid dependence with long-term opioids: A gray area that needs definition, better understanding, treatment guidance, and policy changes. *J Gen Intern Med* 2020;35(Suppl 3):964–971; doi: 10.1007/s11606-020-06251-w
 41. Chou R, Ballantyne J, Lembke A. Rethinking opioid dose tapering, prescription opioid dependence, and indications for buprenorphine. *Ann Intern Med* 2019;171(6):427–429; doi: 10.7326/M19-1488
 42. Rudolf GD. Buprenorphine in the treatment of chronic pain. *Phys Med Rehabil Clin N Am* 2020;31(2):195–204; doi: 10.1016/j.pmr.2020.02.001
 43. Neumann AM, Blondell RD, Jaanimägi U, et al. A preliminary study comparing methadone and buprenorphine in patients with chronic pain and coexistent opioid addiction. *J Addict Dis* 2013;32(1):68–78; doi: 10.1080/10550887.2012.759872
 44. Ehrlich AT, Darcq E. Recommending buprenorphine for pain management. *Pain Manag* 2019;9(1):13–16; doi: 10.2217/pmt-2018-0069
 45. Pergolizzi J, Böger RH, Budd K, et al. Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). *Pain Pract* 2008;8(4):287–313; doi: 10.1111/j.1533-2500.2008.00204.x
 46. Sacerdote P. Opioid-induced immunosuppression. *Curr Opin Support Palliat Care* 2008;2(1):14–18; doi: 10.1097/SPC.0b013e3282f5272e
 47. Hallinan R, Byrne A, Agho K, et al. Hypogonadism in men receiving methadone and buprenorphine maintenance treatment. *Int J Androl* 2009;32(2):131–139; doi: 10.1111/j.1365-2605.2007.00824.x
 48. Miura K, Sano Y, Niho S, et al. Impact of concomitant medication on clinical outcomes in patients with advanced non-small cell lung cancer treated with immune checkpoint inhibitors: A retrospective study. *Thorac Cancer* 2021;12(13):1983–1994; doi: 10.1111/1759-7714.14001
 49. Tran PN, Sheng J, Randolph AL, et al. Mechanisms of QT prolongation by buprenorphine cannot be explained by direct hERG channel block. *PLoS One* 2020;15(11):e0241362; doi: 10.1371/journal.pone.0241362
 50. Zajecka JM, Stanford AD, Memisoglu A, et al. Buprenorphine/samidorphan combination for the adjunctive treatment of major depressive disorder: Results of a phase III clinical trial (FORWARD-3). *Neuropsychiatr Dis Treat* 2019;15:795–808; doi: 10.2147/NDT.S199245
 51. Rickli A, Liakoni E, Hoener MC, et al. Opioid-induced inhibition of the human 5-HT and noradrenaline transporters in vitro: Link to clinical reports of serotonin syndrome. *Br J Pharmacol* 2018;175(3):532–543; doi: 10.1111/bph.14105
 52. Roy PJ, Weltman M, Dember LM, et al. Pain management in patients with chronic kidney disease and end-stage kidney disease. *Curr Opin Nephrol Hypertens* 2020;29(6):671–680; doi: 10.1097/MNH.0000000000000646
 53. Pergolizzi JV, Jr., Scholten W, Smith KJ, et al. The unique role of transdermal buprenorphine in the global chronic pain epidemic. *Acta Anaesthesiol Taiwan* 2015;53(2):71–76; doi: 10.1016/j.aat.2015.06.001
 54. Colson J, Helm S, Silverman SM. Office-based opioid dependence treatment. *Pain Physician* 2012;15(3 Suppl):ES231–ES236; doi: 10.36706/ppj.2012/15/es231
 55. Becker WC, Frank JW, Edens EL. Switching from high-dose, long-term opioids to buprenorphine: A case series. *Ann Intern Med* 2020;173(1):70–71; doi: 10.7326/L19-0725
 56. Merlin JS, Khodyakov D, Arnold R, et al. Expert panel consensus on management of advanced cancer-related pain in individuals with opioid use disorder. *JAMA Netw Open* 2021;4(12):e2139968; doi: 10.1001/jamanetworkopen.2021.39968
 57. Degan M, Mousa SA. A narrative review of buprenorphine in adult cancer pain. *Expert Rev Clin Pharmacol* 2020;13(10):1159–1167; doi: 10.1080/17512433.2020.1822163
 58. Crotty K, Freedman KI, Kampman KM. Executive summary of the focused update of the ASAM national practice guideline for the treatment of opioid use disorder. *J Addict Med* 2020;14(2):99–112; doi: 10.1097/ADM.0000000000000635
 59. Kazerouni NJ, Irwin AN, Levander XA, et al. Pharmacy-related buprenorphine access barriers: An audit of pharmacies in counties with a high opioid overdose burden. *Drug Alcohol Depend* 2021;224:108729; doi: 10.1016/j.drugalcdep.2021.108729
 60. Cohen SM, Weimer MB, Levander XA, et al. Low dose initiation of buprenorphine: A narrative review and practical approach. *J Addict Med* 2022;16(4):399–406; doi: 10.1097/ADM.0000000000000945

61. Gudín J, Fudin J. A narrative pharmacological review of buprenorphine: A unique opioid for the treatment of chronic pain. *Pain Ther* 2020;9(1):41–54; doi: 10.1007/s40122-019-00143-6
62. Shulman M, Wai JM, Nunes EV. Buprenorphine treatment for opioid use disorder: An overview. *CNS Drugs* 2019;33(6):567–580; doi: 10.1007/s40263-019-00637-z
63. The ASAM national practice guideline for the treatment of opioid use disorder: 2020 Focused update [published correction appears in *J Addict Med*. 2020 May/June;14(3):267]. *J Addict Med* 2020;14(2S Suppl 1):1–91; doi: 10.1097/adm.0000000000000683
64. Johnson RE, Chutuape MA, Strain EC, et al. A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. *N Engl J Med* 2000;343(18):1290–1297; doi: 10.1056/NEJM200011023431802
65. Mattick RP, Kimber J, Breen C, et al. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev* 2004;3:CD002207; doi: 10.1002/14651858.CD002207.pub2
66. 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; doi: 10.7326/M17-3107
67. Strickland DM, Sorboro J. Adverse effects of regulation on buprenorphine prescribing and its impact on the treatment of opioid use disorder. *J Opioid Manag* 2021;17(7):133–139; doi: 10.5055/jom.2021.0650
68. Department of Health and Human Services. HHS Releases New Buprenorphine Practice Guidelines, Expanding Access to Treatment for Opioid Use Disorder. 2021. Available from: <https://www.hhs.gov/about/news/2021/04/27/hhs-releases-new-buprenorphine-practice-guidelines-expanding-access-to-treatment-for-opioid-use-disorder.html> [Last accessed: July 25, 2022].
69. American Society of Addiction Medicine. Buprenorphine Mini-Course: Building on Federal Prescribing Guidance. 2021. Available from: <https://elearning.asam.org/products/buprenorphine-mini-course-building-on-federal-prescribing-guidance> [Last accessed: July 25, 2022].
70. American Society of Addiction Medicine. ASAM COVID-19 Task Force Recommendation: Caring for Patients During the COVID-19 Pandemic. 2020. Available from: <https://elearning.asam.org/products/caring-for-patients-during-the-covid-19-pandemic> [Last accessed: July 25, 2022].
71. Martin SA, Chiodo LM, Bosse JD, et al. The next stage of buprenorphine care for opioid use disorder. *Ann Intern Med* 2018;169(9):628–635; doi: 10.7326/M18-1652
72. Dahan A, Yassen A, Romberg R, et al. Buprenorphine induces ceiling in respiratory depression but not in analgesia. *Br J Anaesth* 2006;96(5):627–632; doi: 10.1093/bja/ael051
73. Wightman RS, Perrone J, Scagos R, et al. Opioid overdose deaths with buprenorphine detected in postmortem toxicology: A retrospective analysis. *J Med Toxicol* 2021;17(1):10–15; doi: 10.1007/s13181-020-00795-3
74. Carlson RG, Daniulaityte R, Silverstein SM, et al. Unintentional drug overdose: Is more frequent use of non-prescribed buprenorphine associated with lower risk of overdose? *Int J Drug Policy* 2020;79:102722; doi: 10.1016/j.drugpo.2020.102722
75. Sordo L, Barrio G, Bravo MJ, et al. Mortality risk during and after opioid substitution treatment: Systematic review and meta-analysis of cohort studies. *BMJ* 2017;357:j1550; doi: 10.1136/bmj.j1550
76. Hawk M, Coulter RWS, Egan JE, et al. Harm reduction principles for healthcare settings. *Harm Reduct J* 2017;14(1):70; doi: 10.1186/s12954-017-0196-4
77. Lee JD, Grossman E, DiRocco D, et al. Home buprenorphine/naloxone induction in primary care. *J Gen Intern Med* 2009;24(2):226–232; doi: 10.1007/s11606-008-0866-8
78. Center for Substance Abuse Treatment. Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction. Rockville, MD: Substance Abuse and Mental Health Services Administration (US); 2004.
79. Fitzgerald Jones K, Ho J, Sager Z, et al. Sublingual buprenorphine initiation: The traditional method #441. *J Palliat Med* 2022;25(7):1151–1153; doi: 10.1089/jpm.2022.0135
80. Ghosh SM, Klaire S, Tanguay R, et al. 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; doi: 10.1097/CXA.0000000000000072
81. 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; doi: 10.1002/phar.2313
82. 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
83. Klaire S, Zivanovic R, Barbic SP, et al. 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
84. Ahmed S, Bhivandkar S, Lonergan BB, et al. Micro-induction of buprenorphine/naloxone: A review of the literature. *Am J Addict* 2021;30(4):305–315; doi: 10.1111/ajad.13135
85. Button D, Hartley J, Robbins J, et al. Low-dose buprenorphine initiation in hospitalized adults with opioid use disorder: A retrospective cohort analysis. *J Addict Med* 2022;16(2):e105–e111; doi: 10.1097/ADM.00000000000000864
86. Weimer MB, Guerra M, Morrow G, et al. Hospital-based buprenorphine micro-dose initiation. *J Addict Med* 2021;15(3):255–257; doi: 10.1097/ADM.00000000000000745
87. Randhawa PA, Brar R, Nolan S. Buprenorphine-naloxone “microdosing”: An alternative induction approach for the treatment of opioid use disorder in the wake of North America’s increasingly potent illicit drug market. *CMAJ* 2020;192(3):E73; doi: 10.1503/cmaj.74018
88. Thakrar AP, Jablonski L, Ratner J, et al. Micro-dosing intravenous buprenorphine to rapidly transition from full opioid agonists. *J Addict Med* 2022;16(1):122–124; doi: 10.1097/ADM.00000000000000838
89. Centers for Disease Control. Dosing and Titration of Opioids: How Much, How Long, and How and When to Stop?: Applying CDC’s Guideline for Prescribing Opioids. 2022. Available from: <https://www.cdc.gov/opioids/providers/training/dosing.html> [Last accessed July 25, 2022].

90. Edge WG, Cooper GM, Morgan M. Analgesic effects of sublingual buprenorphine. *Anaesthesia* 1979;34(5):463–467; doi: 10.1111/j.1365-2044.1979.tb06325.x
91. Cuschieri RJ, Morran CG, McArdle CS. Comparison of morphine and sublingual buprenorphine following abdominal surgery. *Br J Anaesth* 1984;56(8):855–859; doi: 10.1093/bja/56.8.855
92. Ouellette RD. Buprenorphine and morphine efficacy in postoperative pain: A double-blind multiple-dose study. *J Clin Pharmacol* 1982;22(4):165–172; doi: 10.1002/j.1552-4604.1982.tb02158.x
93. Tigerstedt I, Tammisto T. Double-blind, multiple-dose comparison of buprenorphine and morphine in postoperative pain. *Acta Anaesthesiol Scand* 1980;24(6):462–468; doi: 10.1111/j.1399-6576.1980.tb01584.x
94. Case AA, Kullgren J, Anwar S, et al. Treating chronic pain with buprenorphine—The practical guide. *Curr Treat Options Oncol* 2021;22(12):116; doi: 10.1007/s11864-021-00910-8
95. Hurley RW. Perioperative buprenorphine: Are we asking the right questions? *Reg Anesth Pain Med* 2019;44(5):537–539; doi: 10.1136/rapm-2018-100205
96. Greenwald MK, Johanson C-E, Moody D-E, et al. Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. *Neuropsychopharmacology* 2003;28(11):2000–2009; doi: 10.1038/sj.npp.1300251
97. 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; doi: 10.1093/pm/pny019
98. Haber LA, DeFries T, Martin M. Things we do for no reason™: Discontinuing buprenorphine when treating acute pain. *J Hosp Med* 2019;14(10):633–635; doi: 10.12788/jhm.3265
99. Hansen LE, Stone GL, Matson CA, et al. Total joint arthroplasty in patients taking methadone or buprenorphine/naloxone preoperatively for prior heroin addiction: A prospective matched cohort study. *J Arthroplasty* 2016;31(8):1698–1701; doi: 10.1016/j.arth.2016.01.032
100. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: Risk factors and prevention. *Lancet* 2006;367(9522):1618–1625; doi: 10.1016/S0140-6736(06)68700-X
101. Alford DP, Compton P, Samet JH. Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. *Ann Intern Med* 2006;144(2):127–134; doi: 10.7326/0003-4819-144-2-200601170-00010
102. Weiss RD, Potter JS, Griffin ML, et al. Long-term outcomes from the National Drug Abuse Treatment Clinical Trials Network Prescription Opioid Addiction Treatment Study. *Drug Alcohol Depend* 2015;150:112–119; doi: 10.1016/j.drugalcdep.2015.02.030
103. Substance Abuse and Mental Health Services Administration (SAMHSA). Key Substance Use and Mental Health Indicators in the United States: Results from the 2017 National Survey on Drug Use and Health (HHS Publication No. SMA 18–5068, NSDUH Series H-53). Substance Abuse and Mental Health Services Administration: Rockville, MD, 2018.
104. Harrison TK, Kornfeld H, Aggarwal AK, et al. Perioperative considerations for the patient with opioid use disorder on buprenorphine, methadone, or naltrexone maintenance therapy. *Anesthesiol Clin* 2018;36(3):345–359; doi: 10.1016/j.anclin.2018.04.002
105. Mercadante S, Villari P, Ferrera P, et al. Safety and effectiveness of intravenous morphine for episodic breakthrough pain in patients receiving transdermal buprenorphine. *J Pain Symptom Manage* 2006;32(2):175–179; doi: 10.1016/j.jpainsymman.2006.01.013
106. Greenwald M, Johanson C-E, Bueller J, et al. Buprenorphine duration of action: mu-opioid receptor availability and pharmacokinetic and behavioral indices. *Biol Psychiatry* 2007;61(1):101–110; doi: 10.1016/j.biopsych.2006.04.043
107. Jones HE, O’Grady K, Dahne J, et al. Management of acute postpartum pain in patients maintained on methadone or buprenorphine during pregnancy. *Am J Drug Alcohol Abuse* 2009;35(3):151–156; doi: 10.1080/00952990902825413
108. Oifa S, Sydoruk T, White I, et al. Effects of intravenous patient-controlled analgesia with buprenorphine and morphine alone and in combination during the first 12 postoperative hours: A randomized, double-blind, four-arm trial in adults undergoing abdominal surgery. *Clin Ther* 2009;31(3):527–541; doi: 10.1016/j.clinthera.2009.03.018
109. Kornfeld H, Manfredi L. Effectiveness of full agonist opioids in patients stabilized on buprenorphine undergoing major surgery: A case series. *Am J Ther* 2010;17(5):523–528; doi: 10.1097/MJT.0b013e3181be0804
110. Jalili M, Fathi M, Moradi-Lakeh M, et al. Sublingual buprenorphine in acute pain management: A double-blind randomized clinical trial. *Ann Emerg Med* 2012;59(4):276–280; doi: 10.1016/j.annemergmed.2011.10.021
111. Macintyre PE, Russell RA, Usher KA, et al. 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; doi: 10.1177/0310057X1304100212
112. Quaye A, Potter K, Roth S, et al. Perioperative continuation of buprenorphine at low-moderate doses was associated with lower postoperative pain scores and decreased outpatient opioid dispensing compared with buprenorphine discontinuation. *Pain Med* 2020;21(9):1955–1960; doi: 10.1093/pm/pnaa020
113. Warner NS, Warner MA, Cunningham JL, et al. A practical approach for the management of the mixed opioid agonist-antagonist buprenorphine during acute pain and surgery. *Mayo Clin Proc* 2020;95(6):1253–1267; doi: 10.1016/j.mayocp.2019.10.007
114. 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; doi: 10.1016/j.bja.2019.03.044
115. Kohan L, Potru S, Barrevel AM, et al. Buprenorphine management in the perioperative period: Educational review and recommendations from a multisociety expert panel. *Reg Anesth Pain Med* 2021;46(10):840–859; doi: 10.1136/rapm-2021-103007
116. National Institute of Drug Abuse. Is the Use of Medications like Methadone and Buprenorphine Simply Replacing One Addiction with Another? 2020. Available from: <https://nida.nih.gov/publications/principles-drug-addiction->

- treatment-research-based-guide-third-edition/frequently-asked-questions/use-medications-methadone-buprenorphine-simply-replacing [Last accessed: July 25, 2022].
117. Robbins JL, Englander H, Gregg J. Buprenorphine microdose induction for the management of prescription opioid dependence. *J Am Board Fam Med* 2021;34(Suppl): S141–S146; doi: 10.3122/jabfm.2021.S1.200236
 118. Cassell EJ. The nature of suffering and the goals of medicine. *Loss Grief Care* 1998;8(1–2):129–142; doi: 10.1300/j132v08n01_18
 119. Jones KF, Ho JJ, Sager Z, et al. Adapting palliative care skills to provide substance use disorder treatment to patients with serious illness. *Am J Hosp Palliat Care* 2022; 39(1):101–107; doi: 10.1177/1049909121999783

Address correspondence to:
Kyle J. Neale, DO
The Lois U and Harry R Horvitz
Palliative Medicine Program
Department of Palliative Medicine
and Supportive Care
Taussig Cancer Institute
Cleveland Clinic
9500 Euclid Avenue, CA5-5
Cleveland, OH 44195
USA

E-mail: nealek@ccf.org