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REVIEW ARTICLE

A Guide to Expanding the Use of Buprenorphine Beyond Standard Initiations for Opioid Use Disorder

James C. Miller[1] · Michael A. Brooks[1] · Kelly E. Wurzel[1] · Emily J. Cox[2] · John F. Wurzel III[1]

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Abstract
Buprenorphine has become an important medication in the context of the ongoing opioid epidemic. However, complex pharmacologic properties and varying government regulations create barriers to its use. This narrative review is intended to facilitate buprenorphine use—including non-traditional initiation methods—by providers ranging from primary care providers to addiction specialists. This article briefly discusses the opioid epidemic and the diagnosis and treatment of opioid use disorder (OUD). We then describe the basic and complex pharmacologic properties of buprenorphine, linking these properties to their clinical implications. We guide readers through the process of initiating buprenorphine in patients using full agonist opioids. As there is no single recommended approach for buprenorphine initiation, we discuss the details, advantages, and disadvantages of the standard, low-dose, bridging-strategy, and naloxone-facilitated initiation techniques. We consider the pharmacology of, and evidence base for, buprenorphine in the treatment of pain, in both OUD and non-OUD patients. Throughout, we address the use of buprenorphine in children and adolescent patients, and we finish with considerations related to the settings of pregnancy and breastfeeding.

1 Background

1.1 History of Opioids, Article Objectives, and Caveats

Opioids are a group of synthetic, semi-synthetic, and naturally occurring compounds derived from the opium poppy plant *Papaver somniferum.* Opioids have been used medicinally by humans for 8000 years for their rapid and potent anti-nociceptive effects [1]. Opioid agonist therapy is the most effective treatment for the worldwide epidemic of opioid use disorder (OUD). Among therapies for OUD, buprenorphine is widely accepted as an important treatment option, and recent steps to deregulate its prescription have made it more accessible. In this environment of expanding availability, the primary objective of this narrative review is to provide a primer on the pharmacology and clinical use of buprenorphine in the treatment of OUD and pain, including standard and low-dose initiation, bridge strategies, and naltrexone-facilitated initiation. Secondary objectives include providing an illustrated guide to the pharmacology of buprenorphine and advocating for increased use of buprenorphine by providers. This review does not cover diacetylmorphine, or the management of patients who have been prescribed high-dose opioid agonists chronically, do not meet the criteria for OUD, and are not interested in transitioning away from full agonist opioids (FAOs). The topic of nonconsensual tapering has been discussed elsewhere [2].

For the purposes of this article, buprenorphine/naloxone sublingual films are treated as the standard for dosing considerations. However, our discussion of buprenorphine applies generally to other sublingual, transdermal, and buccal formulations of buprenorphine, alone or in combination, unless otherwise specified.

1.2 History of the Opioid Use Disorder (OUD) Epidemic

The medical community, governmental agencies, and pharmaceutical companies have all contributed to the OUD epidemic. For most of the twentieth century, prescribers in the United States and many other countries considered opioids contraindicated for the management of chronic pain due to

✉ John F. Wurzel III
john.wurzeliii@providence.org

[1] Psychiatry Residency Spokane, Providence Sacred Heart Medical Center and Children's Hospital, 101 W Eighth Ave, Spokane, WA 99204, USA

[2] Providence Research Network, Renton, WA, USA

risks of tolerance, dependence, and addiction [3]. However, in 1980, Porter and Jick reported new-onset addiction in only four out of > 11,000 patients receiving opioids in the inpatient setting and concluded that "despite widespread use of narcotic drugs in hospitals, the development of addiction is rare in medical patients with no history of addiction [4]." This single-paragraph letter, which argued for the low addictive risk of opioids, was cited over 100 times and helped instigate the subsequent overprescription of opioids.

In the mid-1990s, the concept of pain as the 'fifth vital sign' emerged [5]. Soon thereafter, the Joint Commission and the Veterans' Health Administration both advocated for better routine treatment of pain [5]. Contemporaneously, extended-release oxycodone (OxyContin) was first approved by the US Food and Drug Administration (FDA) in 1995 for managing pain (moderate or severe) that required an opioid for multiple days [6–8]. Subsequently, multiple extended-release opioids were approved, and considered indicated for non-acute pain. Between 1991 and 2013, prescriptions for opioids dispensed by US retail pharmacies increased from 76 million to 207 million, peaking at 219 million in 2011 [6].

In 2001, the FDA directed Purdue Pharma, the manufacturer of OxyContin, to cease making claims that extended-release opioids were less addictive than their immediate-release counterparts [6]. The objectionable language was removed from the drug inserts, but commercial campaigns continued to promote the use of opioids to treat chronic pain and other conditions. In 2007, Purdue Pharma and three individuals were fined US$634 million for off-label marketing amounting to false claims [9, 10].

Regulatory failures, specifically of the pharmaceutical and health care industries, have fueled the opioid epidemic further [11]. In 2022, major US pharmacy retail chains including CVS, Walgreens, and Walmart had settled lawsuits which claimed that they had inappropriately dispensed opioid medications, totaling over US$13 billion [12, 13].

1.3 Epidemiology of OUD

In the early 1980s, lifetime prevalence of heroin use in the US was around 1%, and the 30-day prevalence was typically too low to reliably measure [14]. Heroin users were typically young adults and male, and use was often irregular [15].

As the opioid epidemic developed, patterns of use shifted. The CDC describes three phases of the epidemic, each marked by an increase in overdose deaths [16]. Beginning in 1999, the licit use of prescription opioids rapidly increased, accompanied by an increase in prescription opioid overdose deaths. In response, regulatory changes targeted inappropriate prescribing and the absolute rate of opioid prescriptions in the US peaked in 2012 [17]. Since 2010, incident OUD is increasingly attributable to illicit opioids [15, 18]. In 2010, heroin overdose deaths began to rise as people turned from licit opioids to heroin [16]. Between 2002 and 2018, the prevalence of heroin use and heroin use disorder nearly doubled [19]. Finally, in 2013, synthetic opioid overdose deaths began a steep increase, a pattern which continues to this day [16]. Currently, OUD prevalence is higher in males and highest in people in their late 20s. Some of the highest prevalence of opioid dependence and associated disability-adjusted life-year rates occur in North America, Australasia, and some European countries [20].

We support the trend toward considering OUD as primarily a medical issue rather than a criminal concern. However, it is important to note that this trend, and the privileges that both providers and patients experience because of it, carries racial implications [21]. In the 1960s, the typical new heroin user was a 16.5-year-old male who was about 10% more likely to be White than Black. By the early 2000s, the typical new user was a person in their early 20s of either sex who was overwhelmingly likely to be White (90%) and who transitioned to abuse after using prescription drugs (75%) [15]. Netherland and Hansen hypothesized that the public response to this largely White epidemic has "carved out a less punitive, clinical realm for whites where their drug use is decriminalized, treated primarily as a biomedical disease, and where white social privilege is preserved [21, 22]."

Estimates of OUD prevalence are highly variable. Currently, OUD affects over 2 million individuals in the United States and 16–27 million people worldwide [23]. Millions more people abuse opioids without meeting OUD criteria or receiving formal diagnoses. The genesis of OUD is variable. Patients chronically prescribed opioids have lifetime misuse rates ranging from 3 to 43% [24, 25]. Illicit opioid use can also lead to OUD, though difficulty obtaining accurate data and variable courses of use make accurate incidence rates difficult to calculate [26]. An estimated 23% of heroin or opium users develop dependence, and illicit fentanyl and its derivatives are typically considered even more addictive [27–29]. The mean duration of regular use before remission varies from 4 to 22 years [30, 31].

1.4 Physiology of OUD

Misuse of opioids can lead to OUD, typically a chronic, relapsing-remitting medical disorder that leads to significant distress, functional impairment, morbidity, and mortality [32]. Development of OUD is driven by three main factors. First, opioids are physiologically addictive, and rapid discontinuation of opioid use can lead to uncomfortable withdrawal. Second, by acting on μ-opioid receptors (MORs) in the ventral tegmental area and locus ceruleus, opioids have downstream effects on dopaminergic and noradrenergic neurons, tapping into reward pathways and driving psychological dependence [33, 34]. Third, underlying early life stressors increase vulnerability to addiction by altering

the development of sensory, reward, cognitive and emotive brain systems [35].

1.5 Complications of OUD

OUD represents the largest contributor to disability-adjusted life-years of any illicit drug worldwide [36]. Most of the data related to this subject is derived from heroin-users, although we believe it is likely that fentanyl and its derivatives are equally disabling. Across multiple categories, heroin users have poorer overall health [32]. Opioid use correlates with mental health comorbidities including depression, anxiety, and personality disorders, and co-morbid depression is found in 20–30% of opioid users. Though it is very likely that OUD contributes to these comorbidities, the causality has not been demonstrated, and data also show elevated rates of depression, anxiety, and personality disorders (antisocial and borderline) prior to heroin use. It is likely that the causality is bidirectional. There is conflicting though suggestive evidence that baseline mental health status correlates with worse OUD outcomes [32].

OUD can lead to many infectious complications, particularly when opioids are taken by intravenous or intramuscular routes. In 2013, 18% of people abusing prescription opioids were using by injection [37]. There is little data regarding the routes by which non-prescription opioids are abused, though injection use is common. One major complication of injection use is endocarditis. In 2016, there were over 1.3 million opioid-related inpatient hospital stays in the US. About 10% of those inpatient OUD stays involved endocarditis, representing about 16% of all endocarditis cases [38]. Between 2002 and 2012, the number of hospitalizations involving concurrent opioid abuse/dependence and endocarditis increased by 46.1%. Approximately 50% of endocarditis patients will require heart valve replacement surgery, though unfortunately, up to 20% of patients hospitalized with OUD and endocarditis will leave against medical advice [39].

Other complications of injection use include infections of the bone, joints, skin, soft tissue, or bloodstream, as well as thrombotic and embolic events, vascular injury, botulism, and tetanus. Worldwide, the estimated lifetime prevalence of sepsis among OUD patients is 2–10%, of bone and joint infections is 0.5–2%, and of thrombosis and emboli is 3–27% [40]. Although OUD-specific data is lacking, there are an estimated 155,000 to 540,000 skin infections related to intravenous drug use annually in the United States [41]. Rates of infection with HIV and hepatitis are increased among individuals who use injection drugs [42]. In North America, an estimated 9% of injection users have HIV, 55% have either past or present hepatitis C infections, and 4.8% have active hepatitis B [43]. In a 2011 study of 2489 methadone clinic patients, liver disease (most commonly due to viral hepatitis) occurred at a rate 17 times that found in the general population and was the most common cause of death [44].

1.6 Mortality of OUD Patients

OUD patients have significantly higher mortality rates than the general population. While the crude death rate in the United States is 8–9 per 1000 person-years, one retrospective analysis of ~2600 OUD patients in general treatment settings found a crude mortality rate of 48.6 per 1000 person-years [45]. It also found that overdose of any nature was the most common cause of death among OUD patients. In a meta-analysis of global data, those with OUD were estimated to have a crude mortality rate of 20.9 per 1000 person-years [46].

From 1999 to 2019, opioids were involved (one of possibly multiple substances) in nearly 500,000 overdose deaths (intentional or unintentional) in the US [47]. Moreover, annual opioid-related deaths have continued to rise, from 28,647 in 2014 to 75,673 in the 12 months ending April 2021 [48, 49]. Although rates of death attributable to heroin overdose have been in modest decline since 2018, a simultaneous and dramatic increase in fentanyl-related deaths has driven the overall rate of opioid-related death [16].

Opioid poisoning deaths among children have also increased. Between 1999 and 2016 there was a roughly 270% increase in opioid-related deaths, 80% of which were unintentional. A prescription opioid was implicated in 73% of these deaths, although rates of heroin poisoning among youth aged 15–19 years also increased by over 400% [50].

1.7 Costs to Society

In addition to the human costs, the opioid epidemic inflicts enormous monetary costs. The cost of the opioid epidemic in the US in 2017 was estimated at US$1 trillion, with an average per-case cost of US$221,219 [51, 52]. Between 2005 and 2014, the rate of opioid-related inpatient stays and ED visits in the US increased by 64.1% and 99.4%, respectively [39]. The costs of these ED visits totaled US$328 million in 2017. In Canada, the cost of the opioid crisis in 2014 was around $3.5 billion [53]. In Germany, the total annual cost of treating all 78,500 opioid maintenance treatment patients was estimated at 588.4 million € [54].

2 Treatment of OUD

Treatment of OUD ideally involves pharmacologic management with or without psychosocial interventions. Pharmacological treatments are collectively called medication for opioid use disorder (MOUD), and (medication assisted therapy [MAT] specifically refers to medication with adjunctive psychosocial interventions) [55]. Three medications are used as MOUD in the US, including buprenorphine, methadone, and naltrexone. Evidence about adjunctive psychosocial

interventions for OUD (such as cognitive behavioral therapy, contingency management, and supportive counseling) does not currently support their universal use. A recent systematic review showed no evidence of improved outcomes when psychosocial interventions were added to buprenorphine treatment, though other articles report some evidence suggesting higher rates of abstinence. No studies reported worse outcomes with psychosocial interventions [56]. A 2005 Cochrane review concluded that there was insufficient evidence to draw a conclusion about the effectiveness of psychosocial interventions, though Cochrane has not updated this review. Some of the five studies reviewed showed short-term benefit in treatment engagement compared with control [57]. Another review concluded that psychosocial interventions alone are inferior to methadone [58]. However, many OUD patients have mental health co-morbidities for which psychotherapy is an evidence-based treatment [59].

2.1 Methadone

Methadone is a full agonist at the μ-opioid receptor (MOR). While this contributes to its analgesic efficacy and utility in treating OUD, it also creates risks of misuse and respiratory depression [60]. In the United States, methadone for OUD must be administered in federally approved clinics, which require patients to visit daily or near-daily for at least the first several months of treatment. Methadone clinics are only available in cities that possess both sufficient patients and infrastructure, and they are essentially unavailable in many rural settings. Though less onerous, governmental barriers to methadone exist in multiple other countries as well [61].

One-year retention rates in methadone treatment programs are highly variable and range from 34.4 to 95% [62–64]. Notably, methadone caries a dose-dependent risk of QTc prolongation, with an attendant risk of Torsades de Pointes [60]. For this reason, we recommend a pre-treatment EKG, as well as a review of other potentially QTc prolonging medications.

2.2 Naltrexone

Naltrexone, a long-acting MOR antagonist, blocks the activity of commonly available opioid agonists, thereby preventing intoxication if opioids are used. Studies of oral naltrexone demonstrate only 20% 1-year retention in treatment, compared with 53% retention with long-acting injectable (LAI) naltrexone and 60% retention with buprenorphine and methadone [42]. The different efficacies of the oral and LAI formulations suggest that adherence and a steady plasma level are important.

Initiation of naltrexone requires opioid abstinence for at least a week to minimize the risk of precipitated withdrawal (longer for patients using opioids with longer half-lives). Much of that time may involve significant withdrawal symptoms, leaving patients at high risk for relapse. After this week, a trial of the oral naltrexone is recommended, after which the LAI formulation can be initiated. The antagonism of naltrexone can be overcome by opioid agonists as a function of receptor affinity and concentration. Thus, opioid overdose is still possible for patients taking naltrexone who take enough full agonist opioid (FAO), particularly a high-affinity FAO like fentanyl. Naltrexone is not an option in patients who require opioid therapy for pain management. Naltrexone is also an evidence-based treatment for alcohol use disorder, behavioral addiction disorders, and, in combination with bupropion, methamphetamine use disorder [65, 66].

2.3 Buprenorphine

Buprenorphine is an important treatment for OUD, partially due to its unique pharmacologic profile and partially due to the limitations of the alternatives. A 2014 Cochrane review concluded that buprenorphine (in formulations including sublingual, ethanol solutions, and implants), even at doses as low as 2 mg per day, was superior to placebo in retaining patients in treatment [67]. However, buprenorphine was only effective at reducing illicit drug use at doses of 16 mg or more per day [67]. Low-dose methadone (≤40 mg daily) was superior to low-dose buprenorphine (2–6 mg daily) in treatment retention, but moderate and high doses of buprenorphine and methadone were comparable to each other (at each respective level) in treatment retention and suppression of opioid use [67]. Hypothetically, multiple factors may contribute to this finding. As a FAO, methadone may treat cravings and/or withdrawal more effectively than buprenorphine, methadone clinic structure may provide greater support than typical buprenorphine clinics, and methadone may have appeared superior due to study-specific issues. In the United States, buprenorphine can be prescribed from typical office-based settings and dispensed from nearly any commercial pharmacy. Currently, up to 80% of patients with OUD do not access treatment, and primary care physicians represent the greatest opportunity for expanding access to care [68]. For that reason, buprenorphine is widely viewed as the best option for expanding access to MOUD [69].

Buprenorphine is typically administered as buprenorphine/naloxone combination films or tablets for OUD. The naloxone component is intended to precipitate withdrawal if Suboxone is used via inappropriate routes, which may deter Suboxone misuse [70]. Compared with methadone, illicit use of buprenorphine may be safer, and evidence suggests that buprenorphine diversion frequently occurs for the purpose of withdrawal management rather than abuse [70].

Multiple sources recommend buprenorphine/naloxone for the treatment of OUD in youth, although such treatment

remains underutilized [71, 72]. Timely initiation of MOUD correlates to greater treatment retention among youth with OUD compared with behavioral health services alone [73]. Younger age is also linked to lower rates of continuous MOUD treatment engagement, prompting a recommendation that younger program participants be allowed more flexible dosing and pick-up schedules to minimize drop-out [74]. This recommendation cannot be accommodated in a methadone clinic and renders buprenorphine especially important in the adolescent population.

3 Pharmacology of Buprenorphine

Buprenorphine's efficacy for OUD derives from three characteristics of its MOR activity: (i) high binding affinity, (ii) partial agonism, and (iii) downstream effects on analgesia.

3.1 High Affinity

Buprenorphine possesses a MOR affinity sufficient to displace almost any other ligand. Buprenorphine binding affinity is greater than any morphine derivative or fentanyl, similar to sufentanil, and weaker than carfentanil (which is exclusively used in large-animal veterinary medicine). Buprenorphine has a K_i of 0.21 nM, compared with fentanyl $K_i = 1.346$ nM, methadone $K_i = 3.378$, or oxycodone $K_i = 25.87$ [75] (Table 1). Relative receptor affinities are more difficult to calculate for illicit opioids, many of which are often impure [76]. Clinical evidence suggests that buprenorphine also displays a higher affinity at the MOR than naloxone and naltrexone. We and others have used buprenorphine to 'rescue' patients from naltrexone- or naloxone-induced withdrawal [77–80]. Dozens of emergency departments in California employ buprenorphine to 'rescue' patients from acute withdrawal caused by naloxone treatment for opioid overdose [81]. Overall, buprenorphine effectively outcompetes almost all commonly used FAO and antagonists. However, the degree of buprenorphine MOR occupancy at any given dose, and thus the degree to which it displaces other ligands, is unclear (Table 2).

3.2 Partial Agonism

Although buprenorphine is widely recognized as a MOR partial agonist, the actual degree of agonism is not fully understood. Buprenorphine is less potent than its active metabolite, norbuprenorphine; the parent and metabolite activate the MOR approximately 38% and 81% as much as a FAO, respectively [82, 83]. Though estimates range, half-lives for these compounds are roughly equivalent (31–35 h for sublingual buprenorphine and 34 h for norbuprenorphine) [84, 85]. Thus, averaging the activity of buprenorphine and norbuprenorphine gives an estimate of

Table 1 Pharmacokinetic parameters for mu opioid receptor agonists and antagonists

Drug	Volume of distribution	Bioavailability	Half life	Maximum concentration	Clearance	Key drug metabolizing enzymes	Affinity for μ-opioid receptor (nM)
Sufentanil	1.7 ± 0.2 L/kg	~ 53% (sublingual tablets)	2.5 ± 0.85 h (sublingual tablets)	1 h (sublingual tablets)	12.7 ± 0.8 mL/min/kg	CYP3A4 [182]	0.1380 [75]
Carfentanil	–	–	42 min–5.7 h [183]	–	–	Likely CYP3A4 [183]	0.024 ± 0.04 [184]
Fentanyl	4–6 L/kg	~ 50–76%*	3–4 h (100–200 μg buccal tablet)	47 min (buccal tablet)	–	CYP3A4	1.346 [75]
Methadone	1–8 L/kg	36–100% (oral)	8–59 h	1–7.5 h	–	CYP2B6, CYP2C19, CYP2C9, CYP2D6, CYP3A4	3.378 [75]
Oxycodone	2.6 L/kg	60–87%	3.7 h	1.2–5 h*	–	CYP3A4, CYP2D6	25.87 [75]
Naloxone	–	≤ 2–44%*	0.5–~ 2 h*	~ 15–30 min*	–	UDP-glucuronosyltransferases [185]	–
Diacetylmorphine (heroin)	–	22.9 ± 9.3% (in opioid-naïve subjects) [186]	–	0.10 ± 0.08 (in opioid-naïve subjects) [186]	–	–	–

Information gathered from *Lexicomp*® unless references are otherwise specified

*Depending on formulation

Table 2 Estimates of MOR occupancy based on buprenorphine dose

Dose	Low estimate (%)	High estimate (%)
1 mg [187]	15	29
2 mg [187–189]	28	74
4 mg [187]	45	64
8 mg [187, 189]	78	83
12 mg [187]	76	87
16 mg [188]	79	95
24 mg [187]	85	96
32 mg [187–190]	88	95–98

60% total MOR agonism. While this estimate is accurate enough for practical use, actual exposure to the parent and metabolite varies with dosing schedule, route of administration, concomitant medications, pharmacogenetics, and other factors.

3.3 MOR Agonism and Downstream Signaling

MOR signaling occurs through both a G-protein coupled and a β-arrestin pathway, the latter of which induces MOR internalization via endocytosis [33]. This internalization leads to 'desensitization' which contributes to withdrawal and hyperalgesia in chronic opioid users. Buprenorphine preferentially activates the G-protein coupled pathway, and is thus less likely to produce this desensitization compared with other opioids [33]. Indeed, buprenorphine pre-treatment can prevent MOR desensitization during treatment with other opioids and may reverse desensitization that has already occurred. It is possible that resensitization may happen within minutes of buprenorphine taking effect [86].

3.4 Activity at Other Opioid Receptors

In addition to its activity at the MOR, buprenorphine also acts at δ- and κ-opioid receptors (DOR and KOR), and the opioid-like receptor 1 (OLR-1). At DORs and KORs, buprenorphine is an antagonist. Research on the physiologic role of DORs remains largely preclinical but may involve both nociceptive signaling and mood modulation [33, 87, 88]. Similarly, research on the KOR is primarily preclinical; evidence suggests that KOR antagonists may be helpful in both affective and addiction disorders [89]. Activity at the OLR-1 is discussed below. Overall, although DOR, KOR and OLR-1 are less well understood than MOR, it is likely that buprenorphine's activity at all these sites contributes to its analgesic, affective, and anti-addictive properties.

3.5 Clinical Implications

3.5.1 Ceiling Effect

Due to its partial agonism, buprenorphine exhibits a 'ceiling effect' characterized by an asymptotic dose–response curve. This may limit addictive potential and adverse effects, including respiratory depression (Fig. 1). Compared with methadone, buprenorphine produces a more limited subjective experience of intoxication (including the subscale of 'good effects'), with maximum scores of intoxication approaching a plateau at 8–16 mg (sublingual solution) [90]. While all other opioids are US Drug Enforcement Agency (DEA) schedule I or II controlled substances, characterized as having "high potential for abuse which may lead to severe psychological or physical dependence," buprenorphine is a schedule III controlled substance, described as having "a

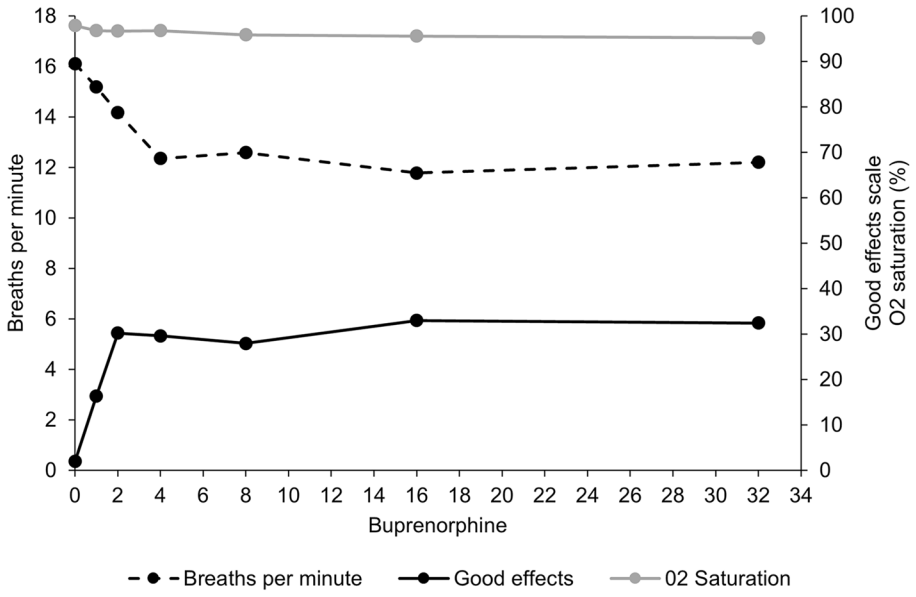

Fig. 1 Illustration of the buprenorphine 'ceiling effect,' which is presumed to protect users against overdose. Buprenorphine produces dose-dependent euphoria ('good effects') and respiratory rate depression which plateau or reach a 'ceiling' at 2 mg and 4 mg, respectively. Across the full clinical dose range, oxygen saturation remains well within normal limits. Data obtained from Walsh et al. [90] using a free plot digitizer (PlotDigitizer Online App)

potential for abuse less than substances in Schedules I or II…" [91]. Though buprenorphine is still physically and psychologically addictive, its partial agonism appears to reduce the risk of these outcomes when compared with FAOs.

The ceiling effect of buprenorphine also provides a measure of protection against overdose. Increasing doses of buprenorphine above 4 mg does not correlate with increasing respiratory depression, and blood oxygen saturation is maintained at all doses through the therapeutic range (Fig. 1). An LD_{50} for buprenorphine has not been experimentally determined in humans. However, based on data extrapolated from animal studies, the therapeutic index of buprenorphine (LD_{50}/ED_{50}) is 12,313, as compared with a therapeutic index of 464 for morphine [92]. Thus, the ceiling effect renders buprenorphine safer in overdose than FAO and allows for the use of much higher doses of buprenorphine than an equipotent full-agonist equivalent.

Because buprenorphine is a high-affinity MOR ligand with a long half-life, it blocks other opioids from accessing the MOR, thus extending its ceiling effect to most other opioids. This property of protecting users from overdose on other opioids is a phenomenon we term an 'umbrella effect,' although data supporting this hypothesis are limited. Some studies do not demonstrate differences between overdose risk in patients maintained on buprenorphine compared with methadone [93, 94]. However, a review of likely opioid overdose deaths in France between 1994 and 1998 found "the yearly estimated death rate related to methadone use was at least 3 times greater than the death rate related to buprenorphine use [95]." A more recent meta-analysis also found a significantly lower overdose mortality in patients taking buprenorphine as compared with those taking methadone (1.4/1000 person-years, 95% CI 1.0–2.0, versus 2.6/1000 person-years, 95% CI 2.1–3.3, respectively) [96]. These limited data suggest that buprenorphine may be protective against overdose when compared with methadone.

3.5.2 Limits of the Ceiling Effect

Buprenorphine overdose, alone or in combination with other CNS depressants (particularly benzodiazepines), is possible [97–101]. Intravenous buprenorphine has also been found to cause respiratory depression in doses utilized for anesthesia (~0.3–0.6 mg), most often when combined with other CNS depressants [102–104]. Accidental ingestion and overdose among children is also of increasing concern, with fatal cases described [105]. Concurrent sedative/hypnotic use increases risk of respiratory depression and may be present in up to 75% of buprenorphine-associated overdose deaths [106]. Patients prescribed benzodiazepines while in buprenorphine treatment have higher treatment retention but also have increased rates of fatal and non-fatal opioid overdose and greater all-cause mortality compared with those not prescribed benzodiazepines [107]. Despite these risks, data suggest that OUD patients taking buprenorphine have a 50% lower all-cause mortality compared with patients who have discontinued buprenorphine [96].

3.5.3 Overdose Risk After Buprenorphine Cessation

Buprenorphine's high-affinity and partial agonism are beneficial for OUD treatment, but these properties also create some challenges. Due to its partial agonism and preferential activation of the G-protein coupled MOR pathway, buprenorphine theoretically causes less opioid tolerance than FAOs [33]. As tolerance is protective against overdose, patients who discontinue buprenorphine and quickly relapse onto previous doses of FAOs may be at an elevated risk of unintentional overdose. Comparative rates of overdose after discontinuation of agonist therapy in patients treated with buprenorphine versus methadone provide some support for this concern. Data from a recent meta-analysis are presented in Table 3 [96]. Patients who had recently discontinued methadone (compared with those who had discontinued more remotely) were at 1.2 times the risk of overdose. However, patients who had recently discontinued buprenorphine (compared with those who had discontinued more remotely) were at 2.6 times the risk of overdose.

3.5.4 Precipitated Withdrawal

Because buprenorphine has significantly higher affinity for the MOR, it will effectively displace all common FAOs from the receptors. Moreover, because buprenorphine is a partial agonist, it will not fully replace the receptor activation provided by FAOs. This creates the risk of an acute decrease in MOR activity, resulting in potentially severe withdrawal symptoms known as precipitated withdrawal [108]. A proposed definition of precipitated withdrawal is an increase in Clinical Opiate Withdrawal Scale (COWS) score of 6 or more within 2 h of buprenorphine initiation [109].

4 Protocols for Buprenorphine Initiation

4.1 Patients Without Recent Opioid Use

Buprenorphine is relatively easy to initiate in patients without recent opioid exposure or risk of withdrawal (Fig. 2). Most patients can begin at a low dose and titrate every few days to a target dose while observing for adverse reactions and efficacy. Dosing regimens vary by formulation (Table 4).

4.2 Patients with Recent Opioid Use

4.2.1 Standard Buprenorphine Initiation

To mitigate the risk of precipitated withdrawal, physicians developed the 'standard initiation' (Fig. 3). In a standard

Table 3 Overdose risk for methadone versus buprenorphine

Mortality metric	Time period	Methadone	Buprenorphine
Overdose mortality/1000 person-years	In-treatment total	2.6	1.4
	First 4 weeks after discontinuation	4.2	10.8
	Beyond 4 weeks after discontinuation	3.4	4.2
	Mortality ratio recent: remote	1.2	2.6
	Out-of-treatment total	12.7	4.6
All-cause mortality/1000 person-years	In-treatment total	11.4	4.5
	First 4 weeks after discontinuation	32.1	32
	Beyond 4 weeks after discontinuation	13.5	10.9
	Out-of-treatment total	36.1	9.5

Data gathered from [96]. The value of 'mortality ratio recent: remote' is calculated as 'first 4 weeks after discontinuation' divided by 'beyond 4 weeks after discontinuation'

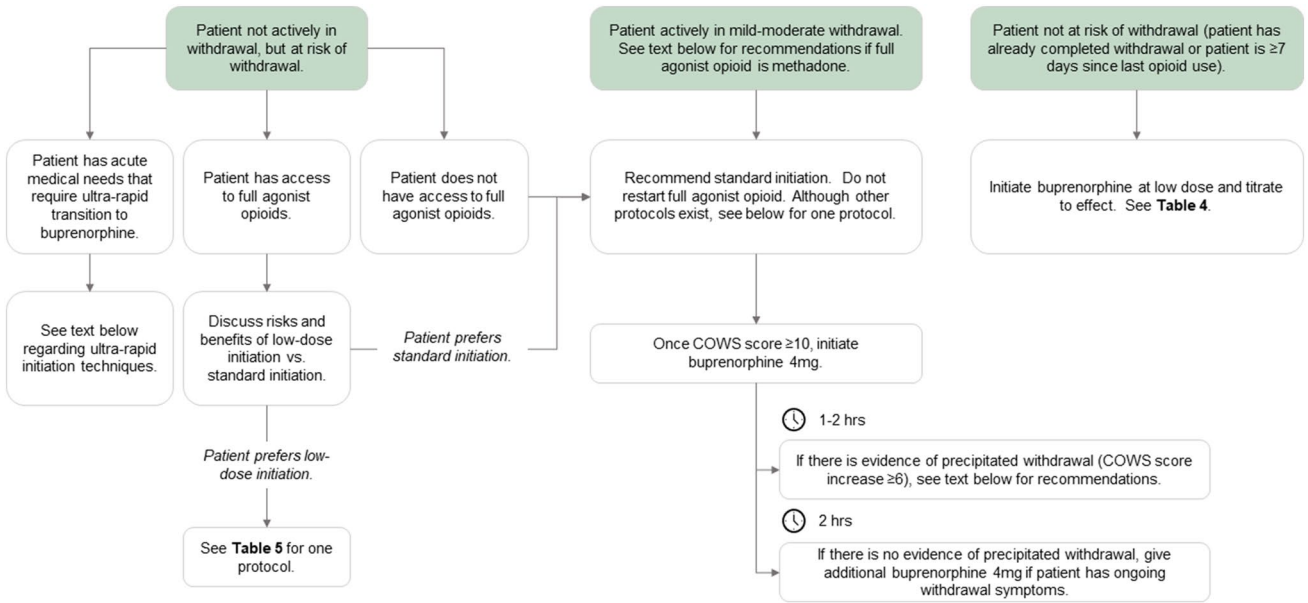

Fig. 2 Protocols for buprenorphine initiation. Flowchart of buprenorphine initiation methods for opioid use disorder in patients without (**A**) or with (**B**) recent opioid use. Standard buprenorphine initiation is currently the most common method in clinical use, but often fails due to the need for a protracted taper from full opioid agonists. Low-dose initiation and bridging are two methods that do not require cessation of full opioid agonists prior to initiating buprenorphine

initiation, the FAO is discontinued and the patient is allowed to go into withdrawal, known as 'planned withdrawal' [110]. When the patient enters mild-moderate withdrawal, it is presumed that there is adequate MOR availability for buprenorphine to bind without acutely displacing too many FAOs. At this point, buprenorphine is expected to increase MOR activity, thus 'rescuing' the patient from withdrawal symptoms [111–113]. During planned (or precipitated) withdrawal, adjunctive agents such as loperamide or bismuth subsalicylate for diarrhea, ibuprofen or acetaminophen for aches, ondansetron for nausea, clonidine for autonomic hyperarousal, and possibly benzodiazepines for anxiety may be used to alleviate withdrawal symptoms. Adjunctive agents with the potential to prolong QTc (including loperamide), should be used with caution.

During a standard initiation, an adequate level of withdrawal to permit safe initiation of buprenorphine is indicated by a COWS score of 5–13 [113–116]. Generally, scores >10 are preferable to minimize the risk of precipitated withdrawal. The initial dose of buprenorphine is generally 2–4 mg; this allows physicians to evaluate the patient after the first dose is given. If the patient experiences an acute worsening of withdrawal symptoms, precipitated withdrawal must be considered and managed as discussed below. If the patient demonstrates ongoing mild-moderate withdrawal or experiences an improvement in withdrawal symptoms, an

Table 4 Dosing regimens for different buprenorphine formulations

Formulation	Initial dose	Maximum dose	Dose equivalence (treating Suboxone film as the standard)	Bioavailability of buprenorphine[c] (%)	Half-life[†]
Subutex (buprenorphine buccal film)	2–4 mg	24 mg[a]	Not described. Anecdotally treated as 1:1 though the bioavailability is different	46–65	27.6 ± 11.2 h
Suboxone film (buprenorphine/naltrexone sublingual film)	2 mg/0.5 mg–4 mg/1 mg	24 mg/6 mg[a]	N/A		
Suboxone tablet (buprenorphine/naloxone sublingual tablet)	2 mg/0.5 mg–4 mg/1 mg	24 mg/6 mg[a]	8 mg/2 mg Suboxone tablet = 8 mg/2 mg Suboxone film	29	~37 h
Cassipa (buprenorphine/naloxone sublingual film)	[b]	[b]	16 mg/4 mg Cassipa = 16 mg/4 mg Suboxone film		
Bunavail (buprenorphine/naloxone buccal film)	2.1 mg/0.3 mg	12.6 mg/2.1 mg	4.2 mg/0.7 mg Bunavail = 8 mg/2 mg Suboxone film	46–65	27.6 ± 11.2 h
Zubsolv (buprenorphine/naloxone sublingual tablet)	2.9 mg/0.71 mg	17.2 mg/4.2 mg	5.7 mg/1.4 mg Zubzolv = 8 mg/2 mg Suboxone film	29	~37 h

Dosing recommendations are from package inserts

[a]Doses > 24 mg of sublingual buprenorphine per day have not shown statistical clinical advantage, but doses of 32 mg per day are commonly used in clinical practice

[b]Cassipa should be initiated once a patient has been titrated to a buprenorphine dose of 16 mg/day on another product. Should further titration be necessary, switch to another product

[c]Data from Lexicomp

additional 2–4 mg is given, with subsequent re-evaluations and repeat doses as indicated.

The generally accepted maximum dose of buprenorphine on the first day is 8 mg to allow for evaluation of adverse effects prior to further dose escalation. This dose may not ameliorate all withdrawal symptoms, but most patients find their symptoms tolerably managed until re-evaluation and potential dose escalation the following day. However, doses > 8 mg can be given on the first day to patients with high opioid tolerance and ongoing intolerable withdrawal symptoms that are improving with buprenorphine treatment [111–113, 116]. This standard initiation is widely accepted and practiced, taught by the US Substance Abuse and Mental Health Services Administration (SAMHSA), and included in the American Society of Addiction Medicine practice guidelines for use of buprenorphine.

Transitioning from FAOs with long half-lives, particularly methadone, can be especially challenging as it takes longer for the FAO to dissociate from the MOR. While 12–24 h of abstinence is typically adequate to produce the necessary mild-moderate withdrawal symptoms in patients using FAOs with short half-lives, methadone requires a minimum of 3 days. Moreover, the pre-initiation dose of methadone should not be higher than 40 mg; 30 mg is more commonly recommended [109]. Thus, patients must taper from treatment doses of methadone to 30 mg, discontinue methadone, wait 72 h, and then initiate buprenorphine. Although many patients experience mild-moderate withdrawal well before the 72 h has elapsed (and frequently before methadone is even discontinued), buprenorphine should not be initiated until 72 h after discontinuation due to the risk of precipitated withdrawal. Though there is no clear guidance in the literature, long-acting formulations with depot-release mechanisms (such as the fentanyl patch) will also likely require longer durations before buprenorphine can be initiated. The specific duration will vary with dosage, formulations, and patient-specific characteristics. Clinicians must simply wait until the patient has entered mild-moderate withdrawal as described above.

4.2.1.1 Drawbacks to the 'Standard Initiation': Why Providers Hesitate to Initiate Buprenorphine

A combination of factors may make patients and prescribers feel hesitant to initiate buprenorphine, a hesitancy which this review seeks to remedy. Patients or providers may find the process of waiting for mild-moderate withdrawal, followed by multiple doses and re-assessments, too complex or confusing (especially given that many of these initiations occur at home without direct physician supervision). They also may be concerned about precipitated withdrawal and may find

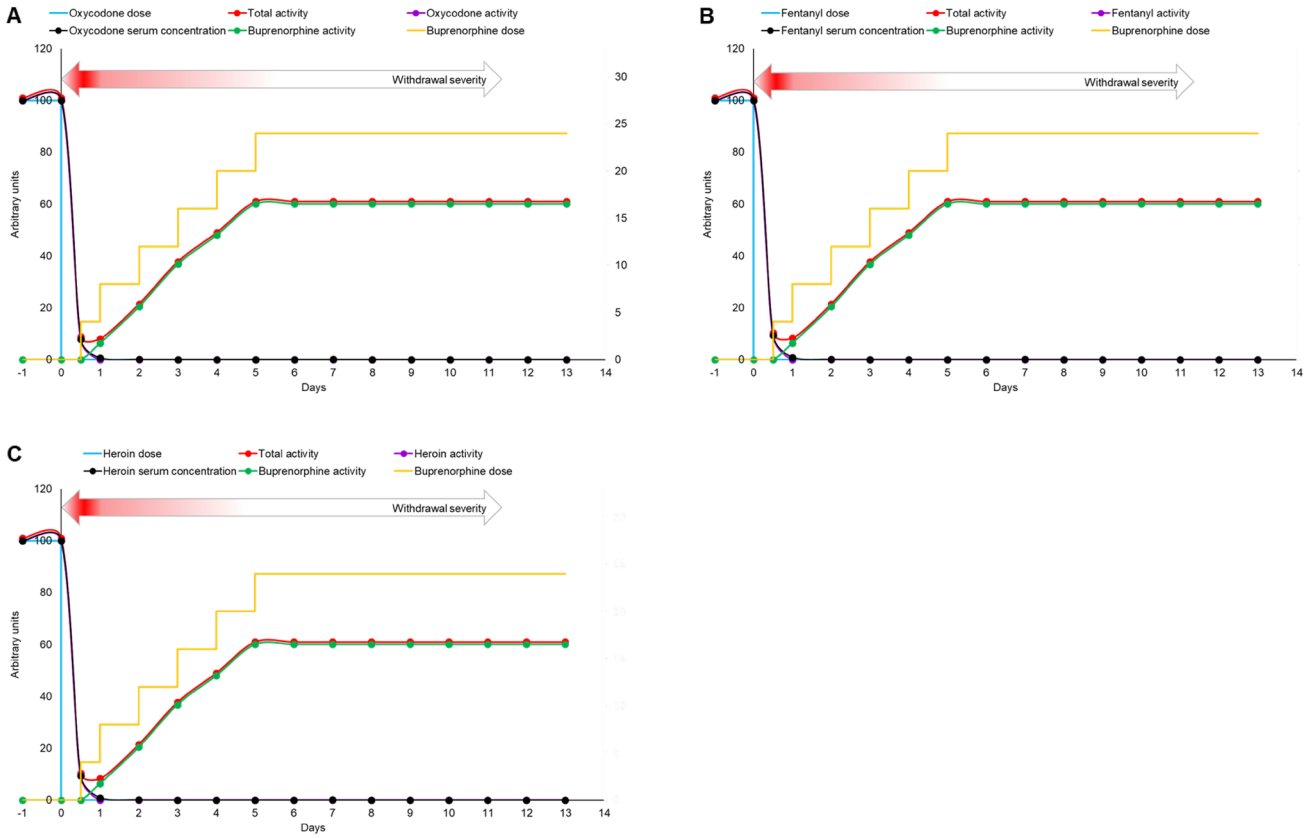

Fig. 3 Representative pharmacology of transition from short-acting full opioid agonists to buprenorphine via standard initiation. Conceptual illustration of the pharmacodynamics of a standard buprenorphine induction after cessation of **A** fentanyl, **B** heroin, and **C** oxycodone. For each full agonist, a rapid decline in serum concentrations is likely to produce planned withdrawal, which is then 'rescued' by initiation of buprenorphine. Calculations are done similarly to those for Fig. 4**,** except that the half-lives of oxycodone, fentanyl, and heroin were set at 3.75 h, 4.5 h, and 0.5 h, respectively

the prospect of planned withdrawal intolerable. Overall, although well-accepted and effective, the standard initiation method has drawbacks that providers may not feel equipped to manage.

First, identifying the timing of 'adequate' withdrawal symptoms is challenging. If the initial dose of buprenorphine is given too early, precipitated withdrawal will result; if the initial dose is given too late, the patient will have suffered unnecessary withdrawal. Although the COWS threshold of > 10 is accepted, that the recommended threshold varies from 5 to 13 suggests a greater degree of uncertainty [114–116]. The point at which adequate MORs are available to permit a buprenorphine rescue varies from patient to patient, driven by factors including the particular FAO of dependence, rate of metabolism (influenced by pharmacogenomics, concomitant medication interactions), and degree of developed tolerance. As a result, both precipitated withdrawal and unnecessary delays in initiation of buprenorphine occur. Indeed, despite the standard initiation protocol being specifically designed to avoid precipitated withdrawal, evidence suggests that it is common. Rates of precipitated withdrawal vary by study, but estimates range from 5 to 16.8% of patients [108, 117]. There is no data on rates of 'unnecessary delay' in buprenorphine initiation, but the effort to minimize precipitated withdrawal likely results in its frequent occurrence.

Second, interpretation of a moderate worsening of withdrawal symptoms after the initial dose of buprenorphine may be difficult, possibly indicating either precipitated withdrawal or inadequately treated underlying withdrawal. No practical method of distinguishing between these possibilities exists. In the inpatient setting, the physician may delay additional buprenorphine treatment to minimize precipitated withdrawal, but if the patient is actually experiencing inadequately treated underlying withdrawal, this delay results in further under-treatment and unnecessary suffering. Alternatively, the physician may provide additional buprenorphine to treat inadequately managed underlying withdrawal, but if the patient is currently experiencing precipitated withdrawal, any additional dosing may worsen the condition (but see the following section on management of precipitated withdrawal). In the outpatient setting, where patients may be

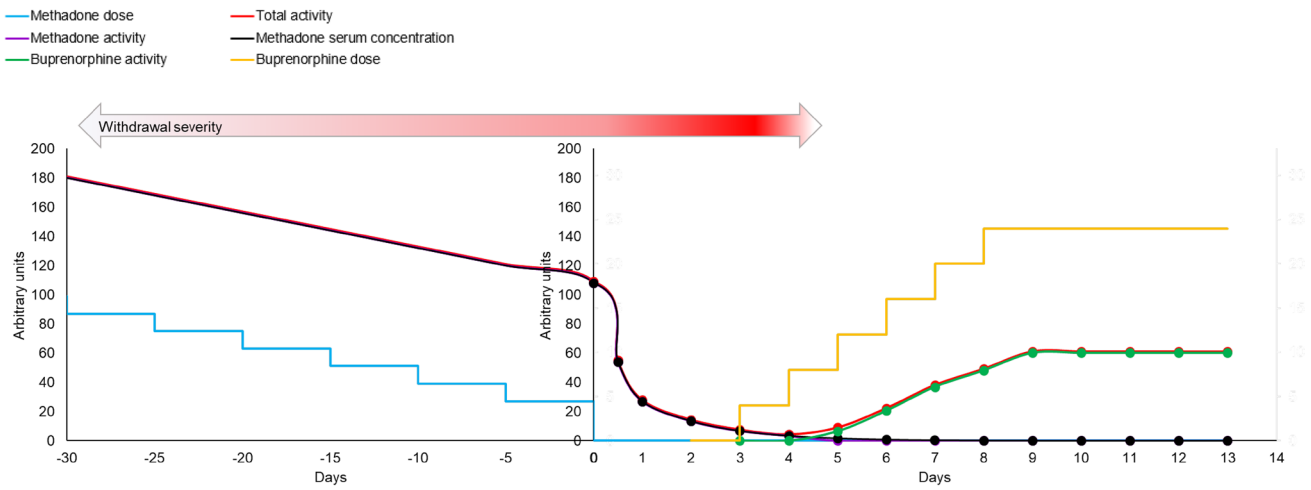

Fig. 4 Representative pharmacology of transition from methadone to buprenorphine via standard initiation technique. Conceptual illustration of the pharmacology of a standard transition from methadone to buprenorphine, prior to which methadone is gradually reduced to 30–40 mg before initiation of buprenorphine/naloxone. A long taper (days −30 to 0) is followed by cessation of methadone at day 0, after which buprenorphine is initiated in escalating doses. All values are representative and given in arbitrary units. The subjective experience of changing opioid tone cannot be numerically quantified, but some values are based on equations as follows: during the gradual taper, methadone activity is presumed to approximate the methadone serum concentration, which in turn approximates the dose from days −30 to 0, and then is eliminated in simple half-lives starting at day 0 such that Methadone serum concentration = [prior concentration]/(2 ∗ half lives per day). Similarly, buprenorphine/naloxone activity cannot be quantified, but increases roughly following the dose to a degree of partial agonism (for the purposes of this graph, ~60% effective concentration). Total activity is the sum of oxycodone activity and buprenorphine plus 1 (an arbitrary vertical offset for visual purposes). Hypothetically, the slope and nadir of the total activity (red line) are most responsible for the subjective experience of withdrawal symptoms. Thus, the standard process of gradually reducing methadone prior to initiation of buprenorphine results in a protracted withdrawal period followed by a rapid worsening in withdrawal symptoms

prescribed buprenorphine for initiation at home, the patient is left with the same potential conundrum.

Third, the standard initiation requires a patient to tolerate significant withdrawal. The duration of this withdrawal is related to the half-life of the FAO. For patients using short-acting FAOs, the period is generally 12–36 h. As illustrated in Fig. 4, the rapid fall in FAO concentration causes withdrawal, which is then 'rescued' by initiation of buprenorphine. The discomfort caused by this transition is a significant drawback to the standard initiation. Although no study specifically evaluates patient retention during the standard initiation process, the START study evaluated 30-day retention in 740 patients who transitioned from short-acting FAOs to buprenorphine via standard initiation [118]. The dropout rate in the first 30 days was 24.8%. In a subsequent qualitative analysis of 67 of the patients who discontinued buprenorphine, 10.4% cited "negative induction experience" as the primary barrier to retention [119]. Withdrawal is protracted for patients using a long-acting FAO such as methadone. Indeed, withdrawal may persist for months (Fig. 4). A prospective study of 33 patients transitioning from methadone to buprenorphine via standard induction found that 20% of patients experienced precipitated withdrawal, and 21% of patients returned to methadone within 1 week of transition [109].

Fourth, precipitated withdrawal reduces success rates with buprenorphine treatment. In a study of 107 standard buprenorphine initiations, patients with 'complicated' initiations (characterized by either precipitated or prolonged withdrawal experiences) had 55.6% treatment retention at 30 days, as compared with 87.6% retention in patients who did not experience a 'complicated' initiation [120]. Another RCT among OUD patients found that higher rates of withdrawal were associated with lower rates of treatment retention [121]. Furthermore, studies suggest an association between severity of withdrawal symptoms and treatment dropout [122]. Precipitated withdrawal may also cause potentially serious medical complications. For example, reports describe cases of Takotsubo cardiomyopathy occurring during opioid withdrawal, including cases precipitated by buprenorphine initiation [123–125].

4.2.1.2 Management of Precipitated Withdrawal Little literature exists to guide the physician in the setting of precipitated withdrawal. In theory, sufficient doses of a high-affinity FAO (such as fentanyl or sufentanil) would be adequate to compete with buprenorphine and alleviate withdrawal symptoms. However, no literature identifies an adequate dose, and the pharmacodynamic activity of the FAO would be unpredictable in the setting of buprenorphine. These factors would combine to put the patient at high risk of unin-

tentional overdose and respiratory depression. Moreover, a 'rescue' with a high-dose FAO runs counter to the goal of initiating buprenorphine treatment, which would need to be repeated from the beginning.

A more common approach is to hold further buprenorphine dosing and manage withdrawal symptomatically with adjunctive medications while waiting for the worst of the precipitated withdrawal to abate [108]. Once the patient has returned to 'normal' withdrawal (a difficult time to identify), buprenorphine dosing can be resumed.

An emerging idea is that precipitated withdrawal may be best managed with additional buprenorphine [108]. There is both indirect and direct evidence supporting this approach. As noted above, buprenorphine is being used in multiple hospitals in California to 'rescue' patients who were treated with naloxone for opioid overdose [81]. Thousands of patients have been treated in this manner and one author describing it states that there is "no need to distinguish between withdrawal from opioid abstinence or withdrawal precipitated by naloxone. Either…state is an acceptable moment to initiate… buprenorphine for OUD [81]." A logical extrapolation of treating naloxone-precipitated withdrawal with buprenorphine is treating buprenorphine-precipitated withdrawal with further buprenorphine. Two case reports describe successful treatment of buprenorphine-precipitated withdrawal with additional buprenorphine. In one case, a patient experienced precipitated withdrawal after receiving buprenorphine/naloxone 4/1 mg; symptoms worsened after an additional 4/1-mg dose, but a third 2/0.5-mg dose (as well as other supportive measures) resulted in acute improvement in the withdrawal symptoms [126]. In the second case, buprenorphine/naloxone 8/2 mg given over an hour precipitated withdrawal; an additional 8/2 mg significantly improved withdrawal symptoms, and yet another 8/2 mg (total dose 24/6 mg during day 1), resulted in symptom resolution [108]. Our anecdotal experience supports this approach, and we typically add enough buprenorphine to bring the total dose to 12–16 mg.

One final consideration when treating buprenorphine/naloxone-induced precipitated withdrawal is the possible contribution of naloxone. Though the sublingual naloxone bioavailability is quite low (estimated at 3%), it is not zero [127]. A study of naloxone concentrations in the urine of buprenorphine/naloxone patients found that 93% of urine samples had naloxone levels above their defined 'clinical cutoff' [128]. Data from Finnish patients involuntarily transitioned from buprenorphine to the buprenorphine/naloxone combination showed that 50% of patients reported adverse effects immediately following the transition and 26.6% of patients continued to report adverse effects at 4 months [129]. One case report describes buprenorphine/naloxone-precipitated withdrawal that resolved entirely with transition to buprenorphine alone [130]. Thus, although unlikely, it is worth considering the possibility that naloxone contributes to any given precipitated withdrawal phenomenon. We do not generally switch patients from buprenorphine/naloxone to buprenorphine monotherapy in this setting, however.

One misconception we have encountered on multiple occasions among patients (and some providers) merits mention here. Patients may misattribute precipitated withdrawal risk and/or side effects of buprenorphine (dysesthesias, headaches, etc.) to the naloxone component. Despite the data above, the majority of the evidence suggests that naloxone is clinically irrelevant when buprenorphine/naloxone is taken correctly. Prescribers should take time to address this misattribution to reduce patients' anxiety, ambivalence, and requests for buprenorphine formulations without naloxone. Furthermore, patients who misattribute the risk of precipitated withdrawal to naloxone may obtain illicit buprenorphine (without naloxone) and unintentionally precipitate withdrawal by taking it. Unfortunately, this experience is often so aversive that patients refuse to consider buprenorphine at future times.

4.2.2 Low-Dose Initiation

By far the best described alternative initiation method is buprenorphine 'low-dose initiation,' also known as the 'microdosing' initiation or the 'Bernese method.' Although no randomized controlled trials of this approach exist, a recent review identified 63 cases across 17 articles [117]. Low-dose initiation utilizes the high affinity of buprenorphine to incrementally displace the FAO over multiple days. In theory, the slow increase in buprenorphine dose prevents this displacement from precipitating withdrawal. Additionally, it has been postulated that rapid MOR resensitization (see previous section 'MOR Agonism and Downstream Signaling') maintains overall opioid tone during a low-dose initiation; as full-agonist opioids are displaced from some receptors, previously internalized receptors may be restored to function [33]. The FAO is continued at full dose until buprenorphine has displaced most or all of it, at which point the FAO may be entirely and abruptly discontinued without taper.

As this technique is relatively new, there is no widely agreed-upon dosing schedule, and the cases reported in the literature vary widely. Generally, buprenorphine doses begin at 0.25–1 mg on day 1 and increase to 8–16 mg over 4–8 days; we use this schedule at our institution (Table 5). Outlier case reports required 3–115 days [117]. Two significant advantages to the low-dose initiation regimen as compared with a standard initiation are reduced complexity and fewer withdrawal symptoms.

Reducing complexity, the low-dose initiation approach avoids any need to estimate 'adequate' withdrawal prior to starting buprenorphine and eliminates ambiguity about

Table 5 Schedule for low-dose buprenorphine initiation

Day	Buprenorphine dose (SL film or tablet)	Full agonist dose
1	0.5 mg BID	Full dose
2	1 mg BID	Full dose
3	2 mg BID	Full dose
4	4 mg BID	Full dose
5	4 mg TID or 8 mg BID	Discontinue full agonist
6+	Titrate to target dose	

Schedule of low-dose buprenorphine initiation used at Providence Sacred Heart Medical Center in Washington state, USA

BID twice a day, *SL* sublingual, *TID* three times a day

moderate withdrawal symptoms. By beginning at a sufficiently low dose, buprenorphine displaces so little of the FAO that the risk of precipitated withdrawal is low. The low-dose initiation protocol should be started while the patient is still using the FAO and the FAO should be continued at full dose until an adequate dose of buprenorphine (8–16 mg) has been reached. The buprenorphine is simply increased, while the dose of the FAO should not be decreased until the end of the protocol. Additionally, there is no complexity in the setting of possible precipitated withdrawal; in the unlikely event of precipitated withdrawal during the low-dose initiation protocol, the buprenorphine must be responsible. The protocol can be decelerated or accelerated as appropriate (see '3.5.4').

Also, the standard initiation requires planned withdrawal, while the low-dose initiation approach is designed to minimize withdrawal. A recent review identified 13 unique cases of low-dose initiation that reported rates of withdrawal. In these cases, mild withdrawal occurred in seven cases (54%) and moderate withdrawal occurred in one case (7.7%) [122]. One case report describes precipitated withdrawal during a low-dose initiation, although the peak reported COWS score was 16, well within the moderate withdrawal range [131]. In a standard initiation, a COWS score of 11 or greater is generally recommended prior to buprenorphine initiation, and the lower cutoff for moderate withdrawal is 12. Thus, all patients will experience mild withdrawal and most patients will experience moderate withdrawal during a standard initiation compared with 54% mild and 5–10% moderate withdrawal during a low-dose initiation [112, 122]. Thus, withdrawal is both more common and more severe in standard initiations. Figure 5 illustrates the pharmacodynamics of a low-dose initiation.

Finally, pain and withdrawal symptoms may be reduced in the setting of low-dose initiation for indirect reasons. In hospitalized OUD patients with acute pain or withdrawal, there is often a tension between minimizing opioid prescribing and providing adequate symptomatic relief. Physicians may be reluctant to prescribe opioids out of concern that they will contribute to addiction. Also, some providers are influenced by the cultural view that addiction represents primarily a moral failure, despite progress in educating prescribers and public alike. For these reasons, some physicians remain reticent to prescribe opioids to patients with OUD. OUD patients actually require higher doses of opioids to ameliorate their symptoms due to tolerance. Pain control and withdrawal treatment are imperative in the short-term, and MOUD is the gold standard for the treatment of OUD in the long-term. Low-dose initiation may relieve this tension as they require continuation of FAOs at full doses, and higher doses of FAOs do not prolong the initiation itself. Therefore, physicians may give themselves 'permission' to be more liberal with FAOs during a low-dose initiation.

Ongoing FAO dosing during low-dose initiation is more challenging for patients taking illicit opioids. For these patients who enter treatment in the inpatient setting, physicians may temporarily prescribe FAOs under close observation to facilitate the low-dose initiation strategy. In the outpatient setting, barriers arise to using a comparable approach. First, accurately identifying the appropriate dose of a prescription FAO to replace the illicit substance, which may be of variable and often unknown composition, is challenging. Second, should the patient continue using illicit opioids atop the prescribed FAO, the risk of overdose may be severe, especially early in the buprenorphine initiation when buprenorphine receptor occupancy is inadequate to provide the 'umbrella' effect. No literature exists describing the use of FAO for this purpose. Therefore, we do not recommend prescription of FAOs to facilitate a low-dose buprenorphine initiation in the outpatient setting for patients using illicit opioids.

Illicit opioid use may thus be a good reason to employ a 'standard' buprenorphine initiation technique or recommend methadone in the outpatient setting. Some patients are unwilling or unable to consider those alternatives, yet may derive significant benefit from buprenorphine. We and others have worked with a few such patients who obtained 3–5 days of their illicit FAO and proceeded with the low-dose initiation [132]. The conversation around this issue is uncomfortable, but the risk entailed in 3–5 additional days of illicit opioid use may be significantly less than ongoing unmedicated OUD. Bridging strategies discussed in the following section are another valid approach, although they are too poorly studied to make any specific recommendations.

In the child and adolescent population, case reports document both efficacy and safety of low-dose initiation protocols when treating either pain or opioid addiction. Two adolescents with chronic pain due to sickle cell disease and without OUD were unable to tolerate standard transitions to buprenorphine due to pain exacerbations. However, they successfully tolerated discontinuation of FAO therapy following

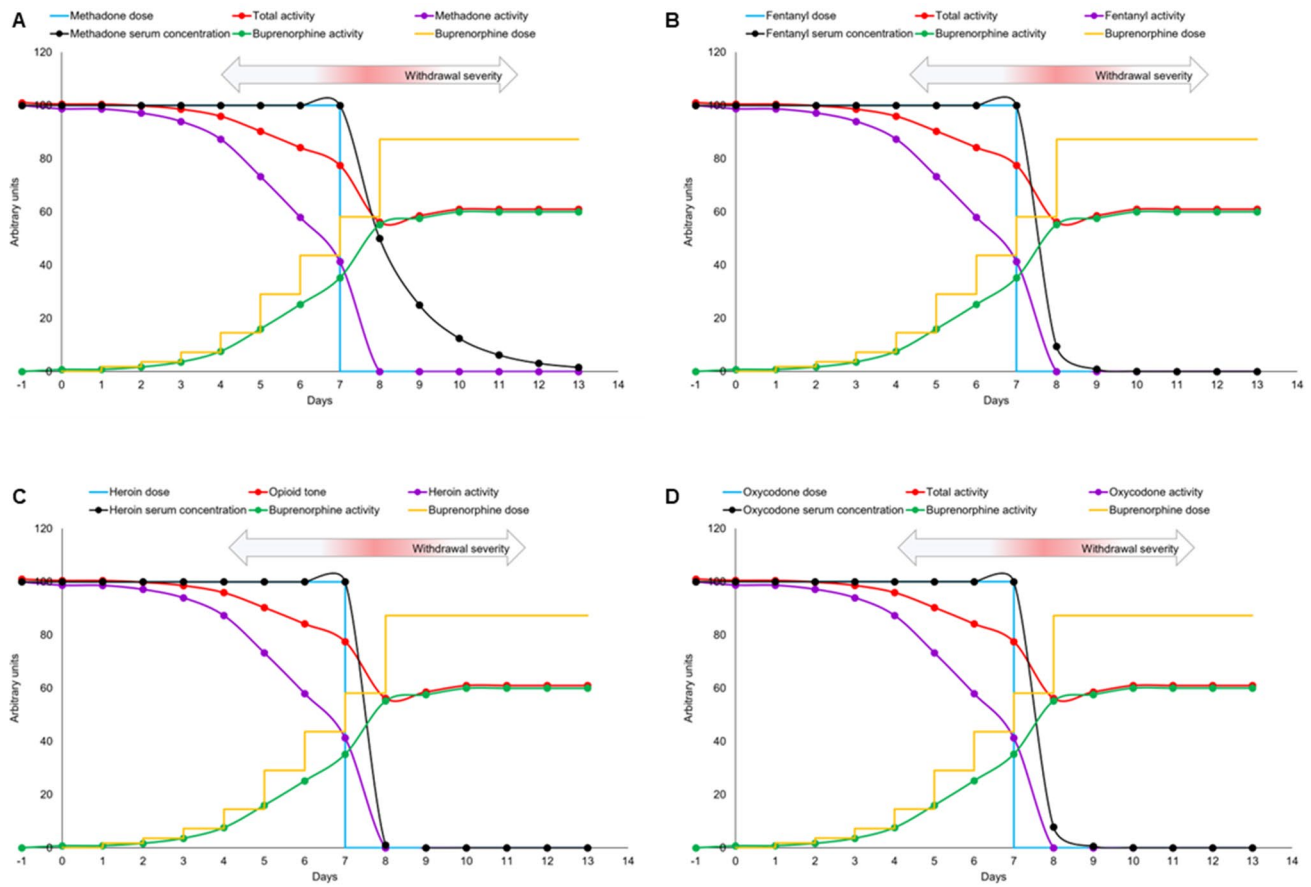

Fig. 5 Representative pharmacology of transition from full opioid agonists to buprenorphine via low-dose initiation. Representative pharmacodynamics of the initiation of buprenorphine after cessation of **A** methadone, **B** fentanyl, **C** heroin, and **D** oxycodone. The red gradient-filled arrow illustrates the severity of withdrawal on a low-dose initiation, which is thought to be less severe than that of the standard induction (Figs. 3, 4). In panel **B**, the dose of fentanyl in arbitrary mass units is too small to render proportionally on the *y*-axis

low-dose initiation over 7–8 days [133]. In another case, a 16-year-old female with severe OUD tolerated a quick transition from hydromorphone to subcutaneous buprenorphine extended-release using a 3-day low-dose initiation protocol. The patient titrated from buprenorphine 0.5 mg on day 1 to buprenorphine 8 mg on day 3, then transitioned to subcutaneous buprenorphine on day 4 [134]. An 11-year-old with chronic pain from sickle cell disease was also able to transition from FAO therapy to buprenorphine via low-dose induction. This child initially required QID dosing for adequate pain relief, as evidence suggests children metabolize buprenorphine at about three times the rate of adults [135].

In summary, low-dose initiation is the principal alternative to standard initiation when transitioning patients from a FAO directly to buprenorphine. Low-dose initiation employs gradually increasing doses of buprenorphine to incrementally displace the FAO; the FAO is continued at full dose until buprenorphine is at an adequate dose to occupy nearly all MORs, at which point the FAO may be abruptly discontinued. Low-dose initiation is less complex than standard initiations and requires less interpretation of potentially ambiguous clinical data. Low-dose initiations are associated with significantly lower rates of withdrawal and may appeal to patients for this reason. However, because low-dose initiation requires access to a FAO throughout, overdose risks limit use of the protocol to controlled treatment environments when the FAO is illicit.

4.2.3 Bridging Strategies

Case reports describe ‘bridging’ strategies in which a third opioid is used to facilitate the transition from FAOs to sublingual or buccal buprenorphine. One strategy uses transdermal buprenorphine as a bridge from FAOs to sublingual or buccal buprenorphine. A second strategy employs transdermal buprenorphine to mitigate withdrawal symptoms during a standard initiation. A third uses a fentanyl patch to bridge from FAOs to buprenorphine. Of note, transdermal

buprenorphine takes a median of 17 h to release 'quantifiable' concentrations (< 24 pg/mL) [136].

4.2.3.1 Buprenorphine Bridging from Full Agonist Opioid to Buprenorphine Therapy Transdermal buprenorphine 'bridging' has been used for various purposes [117, 122]. At the most basic level, it permits lower starting doses during a low-dose initiation. Because the smallest marketed dose of sublingual or buccal buprenorphine is 2 mg, pharmacies may struggle to provide 0.5-mg doses to patients, and doses under 0.5 mg of sublingual or buccal buprenorphine cannot be reliably obtained. Therefore, the use of transdermal buprenorphine, which is dosed in the 120–480 µg/day range, permits lower starting doses. However, such doses are generally unnecessary.

4.2.3.2 Buprenorphine Bridging to Rescue from Precipitated Withdrawal Transdermal buprenorphine also can facilitate a more 'standard' initiation approach (Table 6). In these cases, FAOs are discontinued, a buprenorphine patch is applied at ~12 h, and then sublingual buprenorphine is initiated at ~48 h [122]. Transdermal buprenorphine is administered in low enough doses to ameliorate withdrawal symptoms with minimal risk of precipitating withdrawal. Eleven patients successfully transitioned from methadone 70–100 mg to buprenorphine using a transdermal buprenorphine bridge. Patients discontinued methadone, then received transdermal buprenorphine (35 µg/h) at 12 h. Next, sublingual buprenorphine (2 mg) was initiated at 48 h and was increased through day 5. The transdermal patch was removed on day 4 [137]. Twenty-three inpatients transitioned from short-acting FAOs to buprenorphine in a similar way. FAOs were stopped, a transdermal buprenorphine patch (5 or 20 µg/h) was applied after 12 h, and sublingual buprenorphine (2–4 mg initial dose) followed after 48 h [138]. Of the 34 patients described between the two reports, 27 successfully transitioned to sublingual buprenorphine and the authors report that the approaches were well tolerated with no cases of precipitated withdrawal. Raheemullah and Lembke describe using transdermal buprenorphine in the setting of a FAO taper [139]. COWS scores for patients in their protocol averaged 3.93, below the threshold for mild withdrawal. All patients had refused a standard initiation due to concern about withdrawal.

Table 6 Methodologies for transitions from full agonist to buprenorphine

Hours	0	12	24	48	60	72	84	96	102	109	120
Hess (n=11) [137]											
Full agonist (methadone)	Discontinue										
Transdermal buprenorphine (35mcg/hr)		Apply									
Sublingual buprenorphine (mg)				2	2	8	8	8	8	8	24*
Tang (n=23) [138]											
Full agonist (short acting)	Discontinue										
Transdermal buprenorphine (5-20mcg/hr)		Apply for 24-28 hrs									
Sublingual buprenorphine			2 - 4**								
Raheemullah (n=15) [139]											
Full agonist (not listed for all cases)	Slowly taper							Discontinue after induction complete			
Transdermal buprenorphine (10-20mcg/hr)	Apply for 48 hrs										
Sublingual buprenorphine				≤8†		≤16‡		Titrate to effect			

Legend: Data are gathered from multiple sources [137-139].

* Continue 24 mg daily.

** Titrate "rapidly" by 2-4 mg increments between 2 and 6 days.

† 2 mg test dose. If tolerated 2-4 mg q2-4h. Max dose 8 mg.

‡ Total previous day dose plus 2-4mg q2-4h. Max dose 16 mg.

Data are gathered from multiple sources [137–139]

[a]Continue 24 mg daily

[b]Titrate 'rapidly' by increments of 2–4 mg between 2 and 6 days

[c]2 mg test dose. If tolerated, 2–4 mg every 2–4 h. Max dose 8 mg

[d]Total previous day dose plus 2–4 mg every 2–4 h. Max dose 16 mg

4.2.3.3 Bridging using Other Full Agonist Opioids FAOs have also been used as 'bridging' agents to facilitate the transition from a different FAO to buprenorphine, but case reports are limited. Azar et al. described one patient using both methadone and illicit opioids who was transitioned using a transdermal fentanyl bridge [140]. The patient discontinued both methadone and the illicit opioid and applied a transdermal fentanyl patch. After 5 days, the fentanyl patch was discontinued. Buprenorphine was initiated 12 h later. The patient received a total of 8 mg of buprenorphine in six doses during that day, remained on buprenorphine/naloxone 8/2 mg for the remaining 5 days of hospitalization, and experienced no withdrawal symptoms.

Caulfield et al. transitioned a patient from heroin to buprenorphine in two stages [141]. The patient initially transitioned to slow-release oral morphine plus IV hydromorphone over 49 days. Months later, the patient transitioned from those to buprenorphine over 24 days via a low-dose initiation complicated by multiple missed doses, use of illicit heroin, and precipitated withdrawal due to higher than recommended buprenorphine doses [141].

Vogel et al. report a complicated transition from heroin to buprenorphine via a prescribed diacetylmorphine bridge. Ultimately, the patient was unable to complete the transition, and stabilized on a combination of diacetylmorphine and buprenorphine [142].

4.3 Ultra-Rapid (Naloxone- and Naltrexone-Facilitated) Transition to Buprenorphine

Seven case reports describe ultra-rapid transitions from FAOs, usually methadone, to buprenorphine [77]. In these cases, naloxone or naltrexone is given to precipitate withdrawal from the FAO. After ~ 15–30 min, buprenorphine (4–16 mg) is administered to 'rescue' the patient. All cases took place in the hospital setting. All seven cases described significant and expected withdrawal symptoms following administration of naltrexone or naloxone, a brief period of frank delirium, and rapid resolution of withdrawal symptoms after administration of buprenorphine. In all cases, the transition from methadone to buprenorphine was successfully accomplished in fewer than 24 h and typically fewer than 4 h.

Given the extremity of this intervention, we recommend reserving this approach to situations requiring a very rapid transition. Examples may include patients experiencing dangerous adverse events secondary to methadone and patients for whom alternatives are intolerable. Hypothetically, naloxone/naltrexone may be an unnecessary step, as buprenorphine (which has MOR affinity at least equivalent to that of naltrexone) would simultaneously displace the FAO, induce withdrawal, and rescue the patient.

5 Buprenorphine for OUD and Pain Management

Pain management is a special consideration in buprenorphine patients. Many OUD patients experience acute and chronic pain, and treatment of chronic pain with opioids may lead to OUD. A recent cross-sectional study found that 55% of patients with OUD reported chronic pain [143]. Studies suggest ~ 20% of patients receiving opioids for chronic pain developed aberrant drug-related behaviors, although estimates range from 3 to 45% [3, 144].

Buprenorphine's analgesic use is well described in the anesthesia and pain literature, but is less well described in the OUD literature.

5.1 Pharmacology of Buprenorphine for Analgesia

Buprenorphine is an effective analgesic with unique pharmacologic properties. Studies suggest that buprenorphine exhibits preferential activity at spinal, rather than supraspinal MORs. Analgesia occurs at both the spinal and supraspinal levels, whereas euphoria and respiratory depression are mediated at the supraspinal level alone [145]. Hypothetically, this selectivity for spinal MORs renders buprenorphine a well-tolerated analgesic. Buprenorphine's agonism at the OLR-1, which is also found in peripheral nociceptive pathways, further contributes to analgesia outside of the central nervous system.

In addition to direct analgesic effects, buprenorphine also exhibits anti-hyperalgesic activity. Buprenorphine preferentially activates the G-protein mediated pathway rather than the β-arrestin pathway at the MOR. This results in decreased MOR internalization, leading to greater receptor availability [33, 145]. Ultimately, increased MOR availability facilitates analgesic efficacy while potentially preventing (or even reversing) the development of opioid-induced-hyperalgesia (OIH) [146]. Buprenorphine is also a KOR antagonist, allowing it to effectively compete with the endogenous KOR agonist spinal dynorphin. Spinal dynorphin levels increase with opioid exposure and are known to contribute to OIH. Thus, blocking spinal dynorphin activity is another mechanism by which buprenorphine may prevent and/or reverse OIH [146]. Direct experimental studies suggest that buprenorphine displays significantly greater anti-hyperalgesic properties than the FAOs fentanyl and alfentanil, supporting the suggestion that buprenorphine may minimize or reverse hyperalgesia [147].

One potential limitation of buprenorphine as an analgesic agent would be a ceiling effect imposed by its partial agonism. As discussed above, such a ceiling effect

exists for euphoria, respiratory suppression, constipation, and other adverse effects; authors have suggested such a ceiling effect may pertain to analgesia as well [148]. However, no well-controlled studies have demonstrated such a ceiling effect for buprenorphine's analgesic properties and one small study ($n = 20$, buprenorphine dose 0.2–0.4 mg/70 kg) suggested that no such ceiling effect exists [92, 149, 150]. It appears unlikely that an analgesic ceiling effect exists at traditional analgesic doses. As analgesic dosing is much lower than OUD dosing, it is inappropriate to extrapolate these results. No data currently supports any conclusions regarding the existence of an analgesic ceiling effect at OUD doses.

5.2 Buprenorphine for Pain Management in Patients Without OUD

While a full discussion of buprenorphine for pain management in patients without OUD is beyond the scope of this review, a brief summary follows.

5.2.1 Acute Pain

Multiple studies have evaluated and demonstrated the efficacy of buprenorphine for the management of acute (primarily post-surgical and obstetric) pain in non-OUD patients. Six studies comparing IM buprenorphine to IM morphine, five studies comparing IV buprenorphine to IV morphine, five studies comparing epidural or extradural buprenorphine to epi/extradural morphine, one study comparing sublingual buprenorphine to PCA morphine, one study comparing PCA buprenorphine to PCA fentanyl, and one study comparing sublingual buprenorphine to dihydrocodeine all found buprenorphine to have equal or superior analgesic efficacy relative to the comparator. Doses of buprenorphine varied by study but were generally in the 0.2–0.6 mg range [149]. One study found that sublingual buprenorphine 0.8 mg provided equal analgesic effect to morphine 8 mg but less analgesia than morphine 16 mg [151]. A study of 50 Caesarean section patients treated with buprenorphine in the immediate post-operative period found that 100% of them attained complete pain relief at doses of 7 mg or less of IV buprenorphine. This study found no changes in arterial oxygen or carbon dioxide concentrations or pH when compared with a control and no clinical evidence of respiratory depression, although 8% of the patients displayed 'slight drowsiness' for 30–60 min [152].

5.2.2 Chronic Pain

Multiple studies have evaluated the efficacy of buprenorphine in the management of chronic pain in non-OUD patients. Two studies of buprenorphine in cancer pain found buprenorphine to be superior to placebo, while another study found buprenorphine to outperform sustained-release morphine [153, 154]. A fourth study showed buprenorphine was as effective as oral morphine in the management of cancer pain [154]. A fifth study found buprenorphine to be less effective than tramadol in management of malignant pain [155]. In the management of low back pain, five studies demonstrate buprenorphine is more effective than placebo [156]. Two studies demonstrate that buprenorphine is as effective as FAOs (including morphine sulfate, oxycodone, and fentanyl) in the management of mixed chronic non-malignant pain [157, 158]. Both transdermal and sublingual buprenorphine have been used for analgesia in the pediatric population. Sublingual buprenorphine 2 mg three times a day provided significant pain relief to one 16-year-old girl with severe epigastric pain and odynophagia related to her tumor and radiation esophagitis [159]. The preponderance of evidence suggests that buprenorphine at analgesic doses is more effective than placebo and as effective as FAOs in the management of chronic malignant and non-malignant pain.

5.3 Buprenorphine for Pain Management in Patients with OUD

Unfortunately, the analgesic literature is difficult to apply directly to the OUD population because of differences in dosing, bioavailability, and questions about the existence of a ceiling effect at OUD doses. Maximum analgesic doses of buprenorphine are in the range of 480–1800 μg/day, while OUD doses can approach 20 times that range (Table 4). While OUD formulations include sublingual films and tablets and buccal films, analgesic buprenorphine is typically dosed transdermally or buccally. These different routes of administration produce differences in bioavailability, which interindividual variability exacerbates [160–165]. We can only presume that buprenorphine analgesic efficacy is greater at OUD doses than at typical analgesic doses.

Given the frequent co-morbidity of OUD and chronic pain, and the fact that management of chronic pain with opioids is one common etiology of OUD, the opportunity to treat both pain and OUD with buprenorphine is promising. Unfortunately, it is also poorly studied. There are only two experimental studies focused on buprenorphine for the management of chronic pain in patients with comorbid opioid dependence. These studies looked at chronic pain patients with opioid dependence who transitioned from FAO treatment to buprenorphine at OUD doses; in both studies, patients reported decreased pain scores after transitioning to buprenorphine [166, 167].

A recent review highlights the anti-suicidal effect that buprenorphine has in patients with chronic pain [168]. Though research is preliminary, two RCTs found significantly reduced suicidal ideation in patients treated with

buprenorphine. Unfortunately, the buprenorphine dosing varied from 0.44 mg daily over 4 weeks to 96 mg once, making the data difficult to apply clinically. Additional studies have shown that buprenorphine is associated with the lowest rates of suicidal intent or behavior when compared with other opioids, and that buprenorphine has antidepressant properties. Pharmacologically, buprenorphine may have anti-suicidal effects through antagonistic activity at the KOR. KOR activation is implicated in dysphoria, depression, and anxiety; as noted above, the endogenous opioid spinal dynorphin acts as an agonist at the KOR and is effectively blocked by buprenorphine.

Despite its effective analgesic profile, some care must be taken when using buprenorphine at OUD doses in the setting of acute pain. Due to its high affinity at the MOR and long half-life, buprenorphine doses above 16 mg generally block adjunctive FAOs, while doses of 8–16 mg likely reduce their effect. Below 8 mg, it is believed that adequate MOR availability remains for FAOs to provide near-normal additional analgesia [169]. Quaye and Zhang [169] discuss the arguments for and against continuation of buprenorphine through the perioperative period. They recommend a dose reduction to 8 mg or less with adjunctive FAOs as indicated. However, each case should be considered individually with an eye toward likely pain requirements, risk of relapse onto illicit opioids, patient preference, etc. An alternative is to increase the buprenorphine dose and manage acute pain with buprenorphine alone.

In summary, buprenorphine's analgesic activity is more complex than simple MOR activity and likely involves maintenance of MOR availability, multiple pathways of antihyperalgesic effects, and spinal activity at OLR1. The little extant evidence suggests that buprenorphine does not display a ceiling effect for analgesia at typical analgesic doses, though no evidence exists regarding an analgesic ceiling effect at OUD doses. Compared with placebo, buprenorphine, at analgesia doses, provides superior analgesia for acute and chronic pain in non-opioid dependent patients. Compared with FAOs, buprenorphine, at analgesic doses, is likely equally or more effective for acute and chronic pain in non-opioid dependent patients. Typical analgesic doses should not interfere with the use of FAOs to manage acute pain in the setting of planned surgical interventions. Limited data supports the use of buprenorphine for comorbid chronic pain and opioid dependence at OUD doses. Buprenorphine may also reduce suicidal ideation in patients with chronic pain and/or OUD, though studies are still preliminary. It is unclear whether OUD doses of buprenorphine provide adequate analgesia during planned surgical interventions, but they would likely interfere with adjunctive treatment with FAOs; current recommendations include reducing the buprenorphine dose to 8 mg daily and using adjunctive FAOs to manage acute pain in this setting.

6 Perinatal Considerations

Per 2017 ACOG committee opinion, early universal screening for OUD, brief intervention, and referral for treatment is recommended in the perinatal period [170]. Treatment in the perinatal period ideally includes MOUD and comprehensive and coordinated prenatal and behavioral health care. Methadone has been used for OUD in pregnant patients since the 1960s [171, 172]. Buprenorphine was first used in pregnant patients in the mid-1990s in Europe and over time buprenorphine treatment in pregnant and postpartum women has become common [173, 174].

6.1 Buprenorphine Versus Methadone

Buprenorphine has several possible advantages when compared with methadone in the perinatal period. Women in the perinatal period deal with special psychosocial and medical factors associated with pregnancy, childbirth, and childcare which can create significant barriers to access to care. A study of postpartum women with OUD investigated factors that influenced medication selection and treatment adherence during pregnancy. Among other findings, mothers highlighted the need for autonomy and choice as well as concerns about loss of custody due to mandatory reporting requirements surrounding substance use in the perinatal period, and noted that many treatment environments did not provide gender-responsive care or were poorly suited to mothers in the early postpartum period or their children [175].

Given these concerns, buprenorphine, which is widely accessible and can be prescribed in an office-based setting, may be preferable to the more highly regulated methadone. Additionally, Neonatal Opioid Withdrawal Syndrome (NOWS) in infants prenatally exposed to buprenorphine is milder and shorter when compared with infants prenatally exposed to methadone. The MOTHER study demonstrated that infants prenatally exposed to buprenorphine required significantly less morphine, a shorter duration of treatment for NOWS, and a shorter hospital stay compared with infants prenatally exposed to methadone [176]. While the MOTHER study had a higher attrition rate in the group of mothers using buprenorphine, a recent Cochrane review comparing children of buprenorphine- versus methadone-treated mothers found no difference in dropout rates or the overall number of infants who required treatment for NOWS [177].

6.2 Buprenorphine/Naloxone Versus Buprenorphine Alone

There is some debate concerning the use of buprenorphine alone (monoproduct) versus buprenorphine/naloxone

combinations during pregnancy. A lack of human safety data on naloxone in the perinatal period has led providers to favor buprenorphine monoproducts. Low levels of naloxone are absorbed sublingually and undergo transplacental transfer in a dose-dependent fashion. That said, the quantity of naloxone transferred to the fetus is minimal [178]. The little data that exist suggest that buprenorphine-naloxone does not affect pregnancy outcomes when compared with other modes of medication-assisted treatment [179]. Furthermore, the possibility of severe precipitated withdrawal should a pregnant woman inject or insufflate buprenorphine/naloxone combination products may pose an unacceptable risk to the fetus, though no data address this question.

Historically, women were routinely switched from combination products to monoproducts during pregnancy. However, many women have taken combination products during the perinatal period for a variety of reasons: not realizing they were pregnant, desiring to reduce the risks of diversion or misuse, or encountering barriers to access for monoproducts. Women using combination products have similar pregnancy outcomes compared to women undergoing treatment with other forms of MOUD, which provides reassurance that remaining on a combination product throughout the perinatal period is likely safe and effective [179]. The clinical decision to prescribe a monoproduct or combination product should be based on each individual patient's history, risk factors, and personal preferences.

Developmental outcomes are of clinical concern when discussing medical interventions in the perinatal period, but data are limited. A prospective study evaluated physical, cognitive, and language development outcomes in children up to 36 months of age and found no significant differences between babies exposed in utero to buprenorphine versus methadone [180].

Use of buprenorphine/naloxone and methadone is compatible with breastfeeding and breastfeeding should be encouraged unless other contraindications exist [170, 181].

6.3 Overall Summary and Recommendations

- Low-dose buprenorphine initiations should be considered in lieu of the standard taper protocol for OUD patients using methadone.
- Buprenorphine can be used to maintain analgesia in OUD patients requiring pain management; however, doses > 16 mg may interfere with FAOs used for analgesia.
- In summary, the protection offered by the ceiling and 'umbrella' effects, in conjunction with its comparable sobriety support, significantly greater ease of accessibility when compared with methadone, low cardiac risk, and promising analgesic profile, make buprenorphine an excellent option for patients with OUDs, pain, or a combination of the two.

Declarations

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