

# Frontline Perspectives on Buprenorphine for the Management of Chronic Pain

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**Abstract:** Due to the prevalence of chronic pain and high-impact chronic pain in the US, a significant percentage of the population is prescribed opioids for pain management. However, opioid use disorder is associated with reduced quality of life, along with fatal opioid overdoses, and is a significant burden on the US economy. Considering the clinical needs of patients with intractable chronic pain and the potential harms associated with prescribed and illicit opioids in our communities, having a deep understanding of current treatment options, supporting evidence, and clinical practice guidelines is essential for optimizing treatment selections. Buprenorphine is a Schedule III opioid with a unique mechanism of action, allowing effective and long-lasting analgesia at microgram doses with fewer negative side effects and adverse events, including respiratory depression, when compared with other immediate-release, long-acting, and extended-release prescription opioids. Due to its relatively lower risk for overdose and misuse, buprenorphine was recently added to the Clinical Practice Guideline for the Use of Opioids in the Management of Chronic Pain as a first-line treatment for chronic pain managed by opioids by the US Departments of Defense and Veterans Affairs, and the Department of Health and Human Services recommends that buprenorphine be made available for the treatment of chronic pain. In this narrative review, we discuss the different buprenorphine formulations, clinical efficacy, advantages for older adults and other special populations, clinical practice guideline recommendations, and payer considerations of buprenorphine and suggest that buprenorphine products approved for chronic pain should be considered as a first-line treatment for this indication.

**Keywords:** opioid analgesics, partial opioid agonists, opioid crisis, chronic pain

## Introduction

In 2021, more than 106,000 Americans died of drug-involved overdoses. Overdose deaths involving prescription or illicitly manufactured synthetic opioids other than methadone (primarily illicit fentanyl) rose to 70,601 in 2021, whereas 16,706 deaths involved prescribable opioids, many of which were found in combination with fentanyl.<sup>1</sup> The US economic cost of opioid use disorder (OUD) and fatal opioid overdoses reached nearly \$1.5 trillion in 2020 primarily due to reduced quality of life from OUD and the value of life lost due to fatal overdose.<sup>2,3</sup> Due to the high prevalence of chronic pain and high-impact chronic pain in the US,<sup>4</sup> a significant percentage of the population is still prescribed opioids for pain management. Considering both the clinical needs of patients with intractable chronic pain and the potential harms associated with prescribed and illicit opioids in our communities, having a deep understanding of current treatment options, supporting evidence, and clinical practice guidelines is essential for optimizing treatment selections. Here, we present a narrative review of the different buprenorphine formulations, clinical efficacy, advantages for older adults and other special populations, and payer considerations of buprenorphine based on the relevant studies identified from PubMed and recent clinical practice guideline recommendations.

## Buprenorphine

Buprenorphine is a partial agonist opioid available in different formulations and doses used in patients who have pain (microgram dosing), OUD (milligram dosing), or both. Since the research of analgesic pharmacology has broadened,

when an opioid is medically indicated, buprenorphine may be considered as first-line therapy for chronic pain that cannot be adequately managed with non-opioid analgesics.<sup>5</sup> Buprenorphine formulations include sublingual tablet, buccal film, intravenous, subcutaneous (injection and implant), and patch (Table 1). Buprenorphine buccal film (BBF, Belbuca<sup>®</sup>) and the buprenorphine transdermal patch (Butrans<sup>®</sup>), Schedule III opioids, are currently indicated specifically for long-term pain management for which non-opioid alternative treatments are inadequate.<sup>6,7</sup>

Unlike most naturally occurring, semi-synthetic, and synthetic opioids, which are Schedule II full  $\mu$ -opioid receptor agonists, buprenorphine exerts a unique multimechanistic effect that has unique properties when compared to other immediate-release (IR), long acting, and extended-release (ER) prescription opioids. Buprenorphine is a high-affinity partial agonist at the  $\mu$ -opioid receptor (OR) and an antagonist at the  $\kappa$ -OR and the  $\delta$ -OR.<sup>8–10</sup> Extending this unique mechanism to clinical practice, antagonism at the  $\kappa$ -OR and  $\delta$ -OR may limit some adverse effects, such as constipation and respiratory depression, which are associated with full  $\mu$ -OR agonists.<sup>10,11</sup> In an experimental human pain model, intravenous and sublingual buprenorphine had a lasting antihyperalgesic effect,<sup>12</sup> an effect likely mediated by antagonism

**Table 1** Approved Buprenorphine Products and Dosage Strengths

Buprenorphine Products	Dosage Form	Indication	Dosage Strengths
Buprenorphine Belbuca <sup>®</sup>	Buccal film	Chronic pain	75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, 900 mcg
Buprenorphine Butrans <sup>®</sup> , also available as generic	Transdermal patch	Chronic pain	5 mcg/h, 7.5 mcg/h, 10 mcg/h, 15 mcg/h, 20 mcg/h
Buprenorphine hydrochloride Buprenex <sup>®</sup>	Injection	Acute pain	0.3 mg
Buprenorphine/naloxone Bunavail <sup>®</sup>	Buccal film	Opioid use disorder	2.1 mg buprenorphine/0.3 mg naloxone 4.2 mg/0.7 mg 6.3 mg/1 mg
Buprenorphine Probuphine <sup>®</sup>	Intradermal implant	Opioid use disorder	74.2 mg buprenorphine (equivalent to 80 mg of buprenorphine hydrochloride)
Buprenorphine Sublocade <sup>®</sup>	Extended-release injection	Opioid use disorder	300 mg and 100 mg buprenorphine, administered monthly
Buprenorphine/naloxone Suboxone <sup>®</sup>	Sublingual film	Opioid use disorder	2 mg buprenorphine/0.5 mg naloxone 4 mg/1 mg 8 mg/2 mg 12 mg/3 mg
Buprenorphine hydrochloride Subutex <sup>®</sup> , also available as generic	Sublingual tablet	Opioid use disorder	2 mg, 8 mg
Buprenorphine/naloxone Zubsolv <sup>®</sup>	Sublingual tablet	Opioid use disorder	0.7 mg buprenorphine/0.18 mg naloxone 1.4 mg/0.36 mg 2.9 mg/0.71 mg 5.7 mg/1.4 mg 8.6 mg/2.1 mg 11.4 mg/2.9 mg
Buprenorphine Brixadi <sup>™</sup>	Extended-release injection	Opioid use disorder	8 mg/wk 16 mg/wk 24 mg/wk 32 mg/wk 64 mg/mo 96 mg/mo 128 mg/mo

at the  $\kappa$ -OR.<sup>13</sup> Buprenorphine is also a low-affinity agonist at the nociceptin opioid receptor (formerly known as opioid receptor-like 1 receptor), which blocks tolerance to analgesia, diminishes reward, and likely contributes to the relatively lower potential for abuse.<sup>8,9,14,15</sup>

Buprenorphine has a high affinity, high potency, and slow dissociation rate at the  $\mu$ -OR allowing for effective and long-lasting analgesia at microgram doses. The lower intrinsic activity may contribute to fewer negative side effects or adverse events, including respiratory depression, when compared to full  $\mu$ -OR agonists.<sup>9</sup> Due to its relatively lower risk for overdose and misuse, in May 2022, buprenorphine was added to the Clinical Practice Guideline for the Use of Opioids in the Management of Chronic Pain as a first-line treatment for chronic pain managed by opioids by the US Departments of Defense and Veterans Affairs.<sup>16,17</sup> In addition, the US Department of Health and Human Services recommends that buprenorphine be made available for the treatment of chronic pain.<sup>5</sup>

## Clinical Efficacy

Three pivotal trials of BBF in the treatment of chronic pain support the long-term safety and efficacy of BBF in these patients. BBF significantly reduced mean pain scores compared with placebo in 2 trials of patients with chronic low back pain.<sup>18,19</sup> In a Phase 3 double-blind, placebo-controlled, randomized-withdrawal study in opioid-experienced patients with moderate to severe low back pain using around-the-clock opioids, BBF resulted in clinically meaningful reductions in pain intensity scores. Opioid doses were initially tapered to  $\leq 30$  mg morphine sulfate equivalent, followed by open-label titration with BBF (150–900  $\mu$ g every 12 hours). Patients achieving adequate analgesia were then randomized to BBF or placebo (withdrawal phase) for 12 weeks. A significantly larger percentage of patients receiving BBF experienced pain reductions of  $\geq 30\%$  and  $\geq 50\%$  ( $P < 0.001$ ).<sup>18</sup> In a similar study in opioid-naïve patients with chronic low back pain requiring around-the-clock analgesia, patients were titrated to a dose of BBF that provided adequate analgesia for  $\geq 14$  days and then randomized to BBF or placebo for 12 weeks. A significantly larger percentage of patients receiving BBF vs placebo experienced a  $\geq 30\%$  pain reduction ( $P = 0.0012$ ), whereas patients receiving placebo experienced an increase in pain scores.<sup>19</sup> In an open-label, single-arm, long-term evaluation of the safety and efficacy of BBF, patients who completed the previous studies underwent a dose titration period of  $\leq 6$  weeks until satisfactory pain relief and tolerability were achieved. Treatment at the optimal dose continued for  $\leq 48$  weeks with a constant mean pain intensity score of 3–4, demonstrating the long-term efficacy of BBF.<sup>20</sup> All 3 studies found that BBF was well tolerated, with nausea being the adverse event reported most frequently and an adverse event discontinuation rate of 12.5%.<sup>21</sup>

A common misconception is that partial  $\mu$ -OR agonism equates to partial efficacy.<sup>9</sup> A systematic review of buprenorphine use in chronic pain reported that buprenorphine is as effective as full  $\mu$ -OR agonists in treating pain.<sup>22</sup> Buprenorphine was found to be safe to use in multiple populations, including those with chronic pain and opioid dependence.<sup>22</sup> Severe adverse events were rare, the adverse events that did occur were manageable, and opioid withdrawal incidence was low (3–6%) due to its partial  $\mu$ -OR activity.<sup>22</sup> A recent meta-analysis reported that buprenorphine effectively reduced pain scores for chronic low back pain when compared with placebo.<sup>23</sup> Buprenorphine has also demonstrated efficacy in acute renal colic pain management.<sup>24</sup>

Opioid conversion or opioid rotation is a strategy used to improve analgesia, reduce side effects, and reduce toxicity and/or tolerance in patients being treated for chronic pain.<sup>25,26</sup> While not an exact science, calculated morphine milligram equivalents (MMEs) are routinely considered by clinicians when determining doses for converting from one opioid to another and may be used to gauge the overdose potential of opioids. Epidemiology data suggest that higher daily MMEs increase the risk of opioid-related overdose, morbidity, and mortality.<sup>27</sup> Thus, total daily MME is a common factor clinicians consider when determining the choice and doses of opioids for managing chronic pain.<sup>28</sup> As buprenorphine is a partial  $\mu$ -OR agonist, it is not associated with the same dose-dependent overdose risk as full  $\mu$ -OR agonists and, therefore, appropriately lacks a mathematical MME conversion. This does not imply that similar opioid-level analgesia cannot be achieved or that patients are not exposed to opioid-related risks; however, buprenorphine has several unique properties that may provide some patients advantages over full  $\mu$ -OR agonists.

Because of buprenorphine's high affinity at the  $\mu$ -OR, there has been concern among clinicians that switching from long-term, high-dose, full  $\mu$ -OR agonists to buprenorphine will precipitate withdrawal.<sup>29</sup> In a randomized, double-blind, double-dummy, active-controlled, 2-period crossover study of BBF in opioid-dependent patients with chronic pain

receiving around-the-clock full  $\mu$ -OR agonist therapy (requiring  $\geq 80$  mg MME with documented withdrawal symptoms following naloxone challenge), Webster et al successfully switched patients to BBF at approximately 50% of the full  $\mu$ -OR agonist dose with no significant differences in pain ratings or increased risk of opioid withdrawal (no difference in mean maximum Clinical Opiate Withdrawal Scale scores;  $P=0.79$ ).<sup>30</sup> In a retrospective electronic medical record analysis of daily numerical rating scale pain intensity scores, daily MME, and dose conversion values in patients with chronic pain, 87.9% of patients were successfully converted from full  $\mu$ -OR agonists to BBF with either no change or an improvement in pain scores.<sup>31</sup> Postconversion daily MME decreased by 85.4% from baseline.<sup>31</sup>

Instructions for switching patients from full  $\mu$ -OR agonists to buprenorphine are included in both the Belbuca and Butrans prescribing information. The instructions indicate that to avoid triggering extended withdrawal, the current daily opioid dose should be gradually tapered to 30 MME or less prior to starting BBF or transdermal buprenorphine.<sup>6,7,32</sup> However,  $\mu$ -OR binding is dose-dependent, and the doses of buprenorphine used for chronic pain are much lower than those used for treating OUD (micrograms vs milligrams) and are less apt to precipitate withdrawal. An expert panel recently concluded that weaning of a full  $\mu$ -OR agonist is not necessary to avoid withdrawal and provided a consensus recommendation for conversion to buprenorphine that does not require tapering of the full  $\mu$ -OR.<sup>9</sup> Recent literature also suggests that microdose cross-tapering is a safe and effective way to avoid opioid withdrawal and uncontrolled pain when transitioning from full  $\mu$ -OR agonists to buprenorphine.<sup>33,34</sup> As buprenorphine microgram doses do not prevent the binding of, or compromise the efficacy of, full  $\mu$ -OR agonists, their concomitant use can be beneficial in the titration phase when converting from a full  $\mu$ -OR agonist to BBF or for pain relief in the postoperative/trauma period.<sup>9</sup>

## Belbuca (Buccal Film) vs Transdermal Buprenorphine Formulation

BBF and transdermal patch are the only buprenorphine products approved by the US Food and Drug Administration for chronic pain;<sup>6,7</sup> all others are only indicated for OUD (Table 1). Although no head-to-head trials of BBF and the transdermal formulation have been conducted, evidence suggests that BBF may have a more favorable tolerability profile, is more effective (eg, greater pain intensity reduction), provides better outcomes (eg, fewer discontinuations), and has greater dosing flexibility to manage pain than the transdermal formulation of buprenorphine.<sup>8,21</sup> In a long-term BBF study of patients with chronic low back pain, an optimal dose between 450 mcg and 900 mcg was reached in 88% of patients.<sup>20</sup> Transdermal buprenorphine is available in doses of 5, 7.5, 10, 15, and 20 mcg/h, which, based on bioavailability and pharmacokinetic metamodeling, has a maximal dosing roughly equivalent to 300 mcg BBF.<sup>35</sup> BBF is available in 7 doses (75, 150, 300, 450, 600, 750, and 900 mcg),<sup>6</sup> providing a wider dosing range and greater flexibility to achieve the individualized optimal dose for pain management.<sup>8</sup> The more expansive dose range of BBF more efficiently provides adequate analgesia for patients previously taking daily doses of full  $\mu$ -OR between 90 and 160 MME,<sup>6</sup> whereas transdermal buprenorphine may not provide adequate analgesia for patients requiring more than 80 MME.<sup>7</sup>

The BioErodible MucoAdhesive (BEMA<sup>®</sup>) buprenorphine delivery system developed for Belbuca provides favorable pharmacokinetics compared with the transdermal patch, as the buprenorphine is more rapidly absorbed and has greater bioavailability via the buccal route. BEMA is a water-soluble polymeric film that adheres to the buccal mucosa and dissolves in minutes.<sup>36</sup> The time to maximum plasma concentration ( $T_{max}$ ) for BBF is 2.5 to 3 hours,<sup>6,36</sup> whereas transdermal buprenorphine has a  $T_{max}$  of 26 hours (Table 2).<sup>7,36</sup> The bioavailability is  $\approx 15\%$  for transdermal

**Table 2** Comparison of Buprenorphine Buccal Film and Transdermal Formulations of Buprenorphine

Buprenorphine Product	Bioavailability <sup>36</sup>	$T_{max}$ <sup>36</sup>	Efficacy Comparison: Reduction in Pain Intensity <sup>21</sup>	
			$\geq 30\%$	$\geq 50\%$
Buprenorphine buccal film (Belbuca)	46% to 65%	2.5 to 3 hours*	64%	40%
Transdermal patch	15%	26 hours <sup>†</sup>	49%	31%

**Notes:** \*Median  $T_{max}$  following single dose administration. <sup>†</sup>Median time for Butrans 10 mcg/h to deliver quantifiable buprenorphine concentrations ( $\geq 25$  pg/mL) was approximately 17 hours.

**Abbreviation:**  $T_{max}$ , time to reach maximum plasma concentration.

buprenorphine and 46% to 65% for BBF.<sup>36,37</sup> Due to the relatively rapid absorption and bioavailability of BBF, it provides quicker therapeutic plasma levels with lower overall dosages, compared with transdermal buprenorphine.

The most commonly reported adverse events ( $\geq 10\%$  of subjects) in those taking BBF include nausea, constipation, and headache, which are common adverse events typically associated with opioids.<sup>21</sup> In the randomized-withdrawal study in opioid-experienced patients, vomiting was the only adverse event reported more frequently with BBF than placebo (5.5% vs 2.3%).<sup>18</sup> In opioid-naïve patients, nausea (10%), constipation (4%), and vomiting (4%) were observed more frequently with BBF than placebo during the double-blind phase.<sup>19</sup> With long-term treatment with BBF, nausea, constipation, and vomiting occurred in 8.3%, 3.9%, and 5.1% of patients, respectively.<sup>20</sup> Dental adverse events occur more frequently with sublingual (reporting odds ratio [ROR] 20.03; 95% confidence interval [CI], 18.04–22.24), buccal (ROR 4.46; 95% CI, 3.00–6.61), and oral (ROR 7.17; 95% CI, 5.03–10.22) routes of administration than with implantable or injectable forms of buprenorphine.<sup>38</sup> However, most cases occur in patients using higher-dose transmucosal buprenorphine products for OUD. These effects can be lessened by swishing water in the mouth after the medicine is completely dissolved and waiting an hour before brushing teeth.<sup>39</sup> In a review of 24 studies that assessed safety, transdermal buprenorphine was also associated with nausea, constipation, and headache, as well as with application site pruritus, application site erythema/skin rash, and hyperhidrosis.<sup>21</sup>

## Older Adults or Special Populations

Adults 65 years and older more frequently experience chronic pain and are more likely to be disabled or have comorbidities.<sup>40</sup> Due to reduced renal function and drug clearance, they may have increased susceptibility to accumulation of medications, greater risk of drug–drug interactions, and a smaller therapeutic window for some medications, including the risk of respiratory depression and overdose with opioids.<sup>28,40</sup> Buprenorphine dosing is not subject to renal clearance, making it a safer choice than full  $\mu$ -OR agonists for older adults and those with impaired renal function.<sup>41</sup>

It was recently reported that there are 20-year trends of increasing drug overdose deaths in older adults (57% of which involved opioids), including a stark increase in unintentional overdose deaths involving opioids (59%).<sup>42</sup> Among patients 65 and older, the rate of opioid-related inpatient and emergency department visits increased by 34% and 74%, respectively, between 2010 and 2015.<sup>40</sup> Although drug overdose is an uncommon cause of death among adults older than 65 in the US, the quadrupling of fatal overdoses from 2002 to 2021 (from 3.0 to 12.0 per 100,000) among older adults should be considered in evolving treatment algorithms focused on addressing the overdose epidemic.<sup>42</sup> From 2019 to 2021, buprenorphine-involved opioid deaths accounted for 2.6% of all opioid-involved deaths, and of those, 2.7% occurred in patients aged 65 years or older.<sup>43</sup>

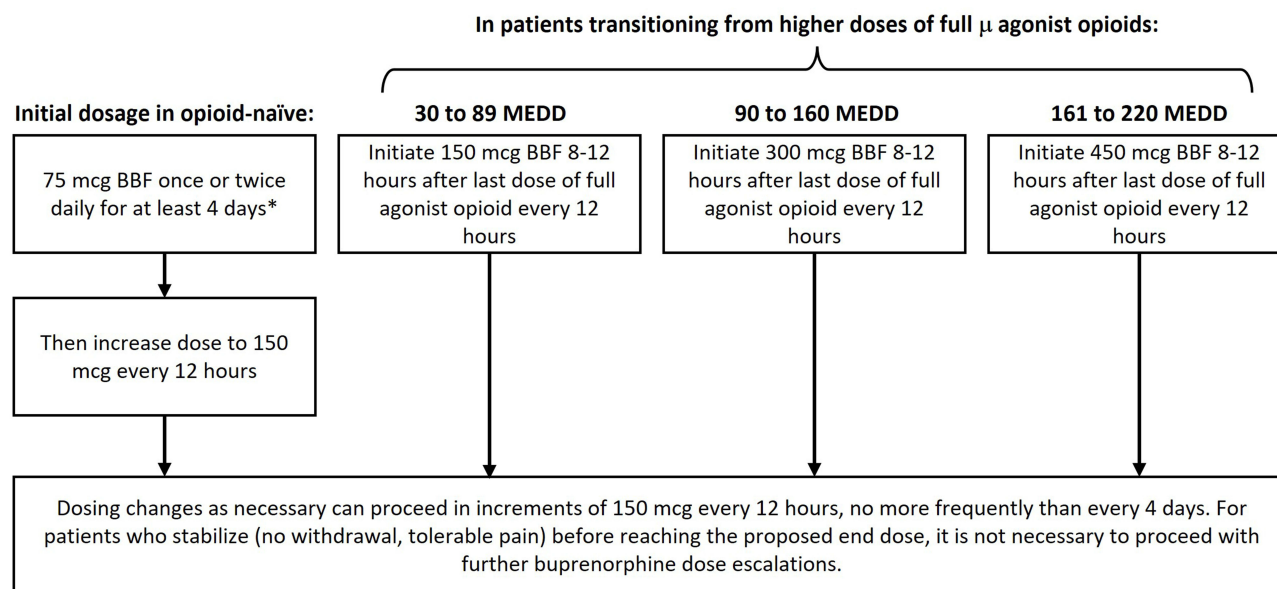
As buprenorphine is extensively metabolized in the liver, in patients with moderate and severe hepatic impairment, higher plasma levels are observed, and buprenorphine has a longer half-life. Therefore, patients with severe hepatic impairment should have initial and titration doses of BBF reduced to half that of patients with normal liver function.<sup>6</sup> Due to concern for accumulation with weekly dosing, transdermal buprenorphine is not recommended in patients with severe hepatic impairment.<sup>7</sup>

The safety and efficacy of buprenorphine for OUD during pregnancy is well established.<sup>44</sup> While there have been no studies of buprenorphine for chronic pain during pregnancy, the fetal safety established in several OUD studies<sup>45,46</sup> suggests that the generally lower doses of buprenorphine used for pain are at least as safe in this population.<sup>47</sup>

## Clinical Practice Guideline Recommendations

Due to its favorable safety profile as a partial agonist at the  $\mu$ -OR, buprenorphine was added to the Department of Veterans Affairs and the Department of Defense (DVADD) Clinical Practice Guideline for the Use of Opioids in the Management of Chronic Pain as a first-line agent in adults with chronic pain compared with full  $\mu$ -OR agonist opioids at moderate to high doses.<sup>17</sup> The recommended approach for initiating or switching to BBF is outlined in [Figure 1](#). The US Department of Health and Human Services (DHHS) guidance notes that if patients on high opioid dosages are unable to taper despite worsening pain and/or function with opioids, whether or not OUD criteria are met, clinicians can consider transitioning to buprenorphine.<sup>32</sup>





**Figure 1** Department of Veterans Affairs and the Department of Defense Recommended Approach for Initiating or Switching to Buprenorphine Buccal Film. Data from the US Department of Veterans Affairs/Department of Defense Clinical practice guideline for the use of opioids in the management of chronic pain; 2022. Available from: <https://www.healthquality.va.gov/guidelines/Pain/cot/VADoDOpioidsCPG.pdf>.<sup>17</sup>

**Abbreviation:** BBF, buprenorphine buccal film.

## Payer Considerations

Many prescription drug coverage policies require therapeutic trials of multiple Schedule II opioids to fail before issuing an approval for payment of buprenorphine for chronic pain.<sup>48</sup> This suboptimal or limited coverage and reimbursement has resulted in a significant access hurdle to buprenorphine treatment for chronic pain, despite its being regarded as a relatively safer and effective opioid.<sup>5</sup> Although a US Drug Enforcement Agency (DEA) X-waiver was never required for prescribing buccal or transdermal buprenorphine for chronic pain, much confusion on this topic has resulted in additional access barriers. Fortunately, the hurdles generated from this misunderstanding and confusion should be eliminated since, as of December 29, 2022, buprenorphine used to treat OUD no longer requires a DEA X-waiver.<sup>49,50</sup>

Due to federal and state regulations, BBF may not be readily available in the pharmacy or formulary.<sup>51</sup> The requirement for prior authorization of opioids also limits the ability of clinicians to prescribe buprenorphine. Additional barriers to clinicians prescribing buprenorphine include misconceptions about competing analgesic effects of concomitant use of short-acting opioids, perceived challenges in perioperative pain management, and transition from an existing regimen with no appropriate mathematical MME conversion factor. There is also a lack of knowledge in opioid conversion to BBF despite evidence that it can be successfully achieved.<sup>30,31,33,34</sup>

Likely secondary to cost implications, payers traditionally appear to favor Schedule II full  $\mu$ -OR agonist formulations over BBF regardless of the potentially higher long-term costs to society, including a higher incidence of overdose, respiratory depression, and adverse events.<sup>48</sup> A Phase 1 study comparing BBF with IR oxycodone suggests that BBF leads to decreased risk of abuse and respiratory depression compared with full  $\mu$ -OR agonists.<sup>52</sup> Buprenorphine has a favorable safety profile, as demonstrated by studies showing a ceiling effect on respiratory depression and gastrointestinal adverse events compared with other opioid treatments and formulations.<sup>36,53,54</sup> Consequently, the US Department of Health and Human Services recommends encouraging the Centers for Medicare & Medicaid Services and private payers to provide coverage and reimbursement for buprenorphine in patients with chronic pain.<sup>5</sup> Payers recommending buprenorphine as a first-line treatment for chronic pain per the US DVADD guidelines may observe

improved safety and efficacy in treating patients with chronic pain while potentially decreasing patient opioid-related harms, with enhanced value by reducing the economic impact of those consequences.

## Conclusions

Buprenorphine provides proven effective analgesia for the treatment of chronic pain. Due to its unique mechanism of action, buprenorphine has a favorable safety and efficacy profile relative to full  $\mu$ -OR agonists. Although somewhat limited by a lack of head-to-head trials comparing BBF and the transdermal formulation, the buccal formulation offers several advantages, such as dose range and bioavailability. As the US economic cost of OUD and fatal opioid overdose is likely to continue to increase,<sup>3,55</sup> prescribers and payers must be educated that BBF offers analgesia with less risk of abuse and respiratory depression than other opioids. Although conversion from full  $\mu$ -OR agonists to buprenorphine has been proven effective in the chronic pain population, further research evaluating tapering strategies and conversion may alleviate some of the hesitation among clinicians to switch patients to buprenorphine. Consistent with the DVADD guidelines and US Department of Health and Human Services recommendations, buprenorphine products approved for chronic pain should be considered as a first-line treatment for this indication.

## Acknowledgments

This review was funded by Collegium Pharmaceutical, Inc. Technical and editorial support for this manuscript were provided by MedLogix Communications, LLC, and funded by Collegium Pharmaceutical, Inc.

## Author Contributions

All authors made a significant contribution in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosures

TMS: Speakers' bureau for Averitas, Salix, AbbVie, Impel; consultant for Collegium. AZ: Speaker's bureau for Averitas; speaker/consultant for Collegium. JA: Speaker for Collegium; consultant for Averitas, Neurometrix, Saluda. The authors report no other conflicts of interest in this work.

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