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Buprenorphine buccal film for chronic pain management

Martin Hale^{*1}, Joseph Gimbel² & Richard Rauck³

¹Gold Coast Research, LLC, 499 NW 70th Ave #200, Plantation, FL 33317, USA

²Arizona Research Center, 15601 N 28th Ave #100, Phoenix, AZ 85053, USA

³Carolinas Pain Institute, 145 Kimel Park Dr #330, Winston-Salem, NC 27103, USA

*Author for correspondence: Goldcoast@halemd.com

Practice points

- On the basis of efficacy and tolerability, buprenorphine is preferable over other opioids for the treatment of chronic pain.
- To date, two buprenorphine formulations are approved by the US Food and Drug Administration for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate: buprenorphine buccal film (Belbuca[®], BioDelivery Sciences International, Inc, NC, USA) and the buprenorphine transdermal system (Butrans[®], Purdue Pharma, LP, CT, USA).
- Of these two formulations, buprenorphine buccal film is better suited for certain patients, as there is access to an extended range of therapeutic doses, increased bioavailability and stronger efficacy and safety data.
- In the chronic pain clinical trials assessed here, buprenorphine buccal film demonstrated efficacy in two 12-week double-blind studies, and sustained efficacy was observed in one long-term clinical study.
- Buprenorphine buccal film was considered generally well tolerated in all clinical studies to date, with no cases of respiratory depression reported.
- Comparison across similar clinical studies of opioids in select patients suggests that buprenorphine buccal film provides efficacy similar to that of Schedule II opioids.
- Buprenorphine buccal film should be considered before tramadol (Schedule IV) in some patients on the basis of efficacy and concerns regarding the ultra-rapid or poor metabolism of tramadol.
- Buprenorphine buccal film should be considered a preferential treatment option for chronic pain over the buprenorphine transdermal system, tramadol and Schedule II opioids in some patients.

Buprenorphine is a Schedule III opioid with unique pharmacodynamic and pharmacokinetic properties that contribute to effective analgesia and fewer safety risks than other opioids. This review article focuses on the buccal film formulation, which is preferable to other buprenorphine formulations on the basis of bioavailability, safety and efficacy. The clinical studies reviewed here confirm that buprenorphine buccal film offers effective and continuous pain relief that is generally well tolerated, with no cases of respiratory depression reported in any of the studies. On the basis of these clinical data and individual patient risk/benefit assessments, clinicians should consider utilizing buprenorphine buccal film as a first-line opioid treatment for chronic pain over other buprenorphine formulations or other opioids.

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An estimated 20.4% of adults in the USA experience chronic pain [1]. Long-term therapy with full μ -opioid receptor agonists has become a standard approach to pain management [2,3]. Commonly prescribed Schedule II full μ -opioid receptor agonists include hydrocodone, oxycodone, oxymorphone, morphine, codeine and fentanyl [4]. Rising rates of opioid-related deaths, the risk of serious adverse events and government scrutiny deter clinicians from using these drugs for patients with chronic pain [5].

Buprenorphine is a unique, Schedule III, partial μ -opioid receptor agonist option for pain management. Preclinical studies have confirmed the efficacy, benign side-effect profile and low addictive and dependence potential of buprenorphine, all of which are attributed to the partial agonistic and slow dissociative properties at the μ -opioid

Table 1. Comparison of the buprenorphine transdermal system and buprenorphine buccal film.

	Buprenorphine transdermal system	Buprenorphine buccal film
Bioavailability	~15%	46–65%
Doses available in the USA	5, 7.5, 10, 15 and 20 µg/h	75, 150, 300, 450, 600, 750 and 900 µg
Safety		
Most common adverse events reported by ≥5% of patients	Nausea, headache, application site pruritus, dizziness, constipation, somnolence, vomiting, application site erythema, dry mouth and application site rash	Nausea, constipation, headache, vomiting, fatigue, dizziness, somnolence, diarrhea, dry mouth and upper respiratory tract infection
Most common adverse events leading to discontinuation in clinical studies	Nausea, dizziness, vomiting, headache and somnolence	Nausea, vomiting and liver function test abnormality
Tolerability	Well tolerated	Well tolerated
Efficacy, opioid-naïve trial data/opioid-experienced trial data		
≥30% response rates	53%/49%	62%/64%
≥50% response rates	43%/35%	41%/40%
Average cost per month, lowest to highest available dosage strengths in the USA	\$313–\$817	\$352–\$857

receptor [6,7]. The functions of buprenorphine at other opioid receptors, such as antagonism at the δ - and κ -opioid receptors and agonism at ORL-1, also contribute to a favorable safety and tolerability profile, as well as antidepressant and anxiolytic effects [7,8]. The interactions of buprenorphine at these four opioid receptors contribute to effective analgesia and offer additional advantages over full μ -opioid receptor agonists, including decreased risk of respiratory depression, constipation, immunosuppression and hypogonadism [7–14].

Buprenorphine has a long-standing history of safety and efficacy in chronic pain clinical studies, including those of general chronic pain, osteoarthritis, malignant pain, musculoskeletal pain and chronic low back pain [15–46]. Clinical data also suggest that buprenorphine may be equally effective in men and women, as no differences in plasma levels have been observed between sexes [47,48]. A Phase IV real-world clinical trial demonstrated that buprenorphine has analgesic efficacy comparable with that of the Schedule II opioids morphine, oxycodone and fentanyl in patients with chronic malignant pain [49]. The properties of buprenorphine therefore contribute to effective pain control and an enhanced tolerability profile, which is preferred for chronic pain management when an opioid medication is indicated.

Two buprenorphine formulations are currently approved by the US Food and Drug Administration for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate: buprenorphine buccal film (Belbuca[®], BioDelivery Sciences International, Inc, NC, USA) and the buprenorphine transdermal system (Butrans[®], Purdue Pharma, LP, CT, USA) [50,51]. These formulations overcome absorption issues that have been observed with oral and sublingual administration [7]. The transdermal and buccal film formulations bypass gastrointestinal and hepatic first-pass metabolism, allowing for enhanced bioavailability and potentially reducing the risk of drug–drug interactions [52–55].

Although effective pain control has been demonstrated for 10–70 µg/h of the buprenorphine transdermal system, providers in the USA are limited to a narrow therapeutic dose range of 5–20 µg/h [37,51,56,57]. The 20 µg/h patch may not provide adequate analgesia in patients receiving higher dose opioid treatment (>80 mg morphine sulfate equivalent/d) [51]. Buprenorphine buccal film is available in seven dose strengths (75, 150, 300, 450, 600, 750 and 900 µg) and is intended for use in patients requiring a morphine sulfate equivalent of up to 160 mg/day [50]. The dose range of buprenorphine buccal film provides more flexibility to titrate to an optimal dose and is a preferable option for patients whose therapeutic needs exceed the dosing capability of the buprenorphine transdermal system [44,58]. Compared with the transdermal formulation, buprenorphine buccal film has increased bioavailability, fewer reports of adverse events, generally greater efficacy and a similar price point (Table 1) [50,51,54,59–61]. Thus, the properties of buprenorphine buccal film are preferred for the treatment of chronic pain (Table 1; Figure 1) [45].

Buprenorphine buccal film has advantages over the transdermal formulation and is considered by many practitioners to be a preferential treatment option over Schedule II opioids on the basis of efficacy and safety demonstrated by clinical studies [44–46,62]. This review article is thus focused on the buccal formulation, with the primary objective of providing an overview of the clinical studies that have examined buprenorphine buccal film as a resource for clinicians who are seeking alternative treatments for chronic pain.

Figure 1. Buprenorphine buccal film. Buprenorphine buccal film is a small, bilayered dissolving polymer film that adheres to the buccal mucosa using BioErodible MucoAdhesive® technology, which enhances bioavailability compared with other routes of administration [59]. Buprenorphine buccal film is available in 75, 150, 300, 450, 600, 750 and 900 µg dosage strengths and facilitates a unidirectional flow of the drug that has approximately 46–65% bioavailability and reaches steady-state levels in approximately 3 days [50,54].

Figure 2. Design of buprenorphine buccal film clinical trials in patients with chronic low back pain. The safety and efficacy of buprenorphine buccal film were studied in two double-blind, Phase III, randomized, placebo-controlled trials in (A) opioid-experienced [44] and (B) opioid-naïve [46] patients that comprised a 2-week screening phase; an open-label titration phase; a 12-week double-blind, placebo-controlled treatment phase; and follow-up. An analgesic taper phase was also included for opioid-experienced patients. (C) The long-term study [45] included rollover patients from (A & B) or *de novo* recruits and was comprised of a dose-titration period of ≤6 weeks with buprenorphine buccal film; patients who achieved and maintained an optimal dose (300–900 µg/12 h) for ≥7 days continued treatment for a long-term period up to 48 weeks.

Buprenorphine buccal film clinical trials

Efficacy

Two pivotal Phase III, multicenter, 12-week, double-blind, placebo-controlled, enriched-enrollment, randomized-withdrawal clinical trials evaluated the safety and efficacy of buprenorphine buccal film (75–900 µg/12 h) in opioid-experienced and opioid-naïve patients with chronic low back pain (Figure 2A & B) [44,46]. An additional open-label, single-arm, 48-week study was performed to evaluate the long-term safety and efficacy of buprenorphine

Figure 3. Double-blind studies: buprenorphine buccal film significantly reduced pain intensity scores compared with placebo in patients with chronic low back pain. Primary sensitivity analyses comparing the change from baseline to week 12 in numerical rating scale pain intensity scores in patients receiving placebo compared with those receiving buprenorphine buccal film.

LCL: Lower confidence limit; UCL: Upper confidence limit.

Data taken from [44,46].

buccal film (150–900 µg/12 h) [45]. The open-label study examined opioid-experienced and opioid-naïve rollover patients from the two double-blind studies as well as a third cohort of newly recruited *de novo* patients (Figure 2C) [45].

In the double-blind opioid-experienced study, a total of 810 patients entered the open-label titration phase, 510 of them were randomized and treated ($n = 254$, buprenorphine; $n = 256$, placebo) [44]. In the double-blind opioid-naïve study, 749 patients entered the open-label titration phase, and 461 were randomized and treated ($n = 229$, buprenorphine; $n = 232$, placebo) [46]. In the long-term study, 506 patients entered the titration phase (445 rollover patients and 61 *de novo* patients), and 435 patients entered the long-term treatment phase [45].

The randomized-withdrawal design utilized in the double-blind studies examines efficacy by comparing the increase in pain between those randomized to placebo and those who continue on active study treatment [44]. In the double-blind studies, the primary efficacy end point was change in mean daily average pain intensity scores from baseline (after the open-label titration phase) to week 12 using an 11-point numerical rating scale [44,46].

In opioid-experienced and opioid-naïve patients, numerical rating scale pain scores increased significantly more from baseline to week 12 in those randomized to placebo than in those continuing to receive buprenorphine buccal film ($p < 0.001$ and $p = 0.0012$, respectively; Figure 3) [44,46]. These results indicate that buprenorphine buccal film provided greater pain relief than placebo [44,46]. In addition, the buprenorphine buccal film group in each study had significantly lower pain scores throughout all 12 weeks than the placebo group [44,46].

In the long-term open-label study, efficacy was measured as change from baseline in mean daily average pain intensity scores throughout the titration and long-term treatment phases using an 11-point numerical rating scale [45]. At the start of initial titration, all patients (including rollover patients) received buprenorphine buccal film 150 µg/12 h, regardless of the previous dose, which was then titrated to an optimal dose [45]. In the titration phase, numerical rating scale pain intensity scores briefly increased in rollover patients because of a rapid decrease in dose at the start of the titration phase [45]. During long-term treatment with an optimal dose, mean numerical rating scale scores remained decreased and stable until the end of the treatment phase at week 48, supporting sustained efficacy [45]. In addition, the dose of buprenorphine buccal film remained unchanged in 86.2% of patients over the 48 weeks of treatment, confirming efficacious treatment with an optimal dose and nontolerance.

In the double-blind studies, the proportion of patients who experienced a ≥ 30 or $\geq 50\%$ decrease in numerical rating scale pain intensity scores at week 12 of the double-blind phase was also assessed [44,46]. In the opioid-experienced population, a significantly greater percentage of patients receiving buprenorphine buccal film achieved

Figure 4. Proportion of responders in the double-blind studies. The percentage of patients achieving $\geq 30\%$ (A) or $\geq 50\%$ (B) pain reduction from the period before the open-label titration to week 12 of the double-blind treatment phase.

≥ 30 or $\geq 50\%$ pain reduction compared with the placebo group ($p < 0.001$; Figure 4) [44]. In the opioid-naïve population, a significantly greater percentage of patients receiving buprenorphine buccal film achieved $\geq 30\%$ pain reduction compared with the placebo group ($p = 0.0012$; Figure 4) [46]. However, the proportion of patients achieving $\geq 50\%$ pain reduction was not significantly different between groups ($p = 0.0754$), which was likely due to a higher placebo response in opioid-naïve patients (Figure 4) [46].

To further evaluate the efficacy of buprenorphine buccal film, the use of rescue medication (hydrocodone/acetaminophen or acetaminophen alone) was also determined in both studies [44,46]. In each double-blind study, the placebo group required more rescue medication than the buprenorphine group [44,46]. During the open-label long-term study, the use of rescue medication was low (~ 3.0 tablets per day) during the titration phase and decreased further during the long-term phase (~ 1 tablet per day) [45].

To determine the impact on quality of life in both double-blind studies, patient-reported impression of changes in activity limitation and treatment benefits were measured with Patient Global Impression of Change (PGIC) scores, and low back pain as a health status marker was measured with the Roland Morris Disability Questionnaire (RMDQ) [44,46]. In both studies, change in PGIC scores favored those randomized to buprenorphine buccal film over those randomized to placebo ($p < 0.001$ for opioid-experienced patients and $p = 0.0011$ for opioid-naïve patients) [44,46]. RMDQ scores were lower in the buprenorphine group than in the placebo group in both studies, indicating better function [44,46]. Patient satisfaction with buprenorphine buccal film treatment was also high, as indicated by the percentage of patients completing the double-blind studies who continued in the long-term safety study (445/549; 81.1%) [44–46].

Safety

During open-label titration with buprenorphine buccal film in the double-blind studies, the most common adverse events were those typically associated with opioids, including nausea, constipation, vomiting, headache, dizziness and somnolence (Table 2) [44,46]. Nausea was the most common adverse event, occurring in 49.8% of opioid-naïve patients; however, drug-induced nausea is acute and commonly subsides [44,46,63]. In the long-term study, nausea and constipation occurred during open-label titration, although to a lesser extent than what was observed in the double-blind studies (Table 2) [44–46].

Following open-label titration, the number of adverse events decreased during double-blind treatment [44,46]. Nausea and vomiting occurred in $\leq 10\%$ and constipation in $< 5\%$ of opioid-experienced and opioid-naïve patients receiving buprenorphine buccal film in the double-blind studies; the incidence of these adverse events remained

Table 2. Adverse events occurring in $\geq 5\%$ of patients receiving buprenorphine buccal film during open-label titration in at least one study.

Adverse event, n (%)	Opioid experienced (n = 810)	Opioid naive (n = 749)	Long-term (n = 506)
Gastrointestinal disorders			
Nausea	136 (16.8)	373 (49.8)	52 (10.3)
Constipation	67 (8.3)	97 (13.0)	30 (5.9)
Vomiting	54 (6.7)	58 (7.7)	12 (2.4)
Nervous system disorders			
Headache	54 (6.7)	60 (8.0)	18 (3.6)
Dizziness	42 (5.2)	48 (6.4)	None reported
Somnolence	41 (5.1)	52 (6.9)	None reported

Table 3. Adverse events occurring in $\geq 5\%$ of patients receiving buprenorphine buccal film during the double-blind or long-term treatment studies.

Adverse event, n (%)	Double-blind				Long-term (n = 435)
	Opioid experienced (n = 510)		Opioid naive (n = 461)		Buprenorphine buccal film (n = 435)
	Placebo (n = 256)	Buprenorphine buccal film (n = 254)	Placebo (n = 232)	Buprenorphine buccal film (n = 229)	
Gastrointestinal disorders					
Nausea	19 (7.4)	19 (7.5)	17 (7.3)	23 (10.0)	36 (8.3)
Vomiting	6 (2.3)	14 (5.5)	1 (0.4)	9 (3.9)	22 (5.1)

low during the long-term study (Table 3) [44–46]. Importantly, no cases of respiratory depression were observed in any of the studies [44–46].

Switching to buprenorphine buccal film from a full μ -opioid receptor agonist

An additional double-blind crossover study was performed in an opioid-experienced population (≥ 80 but ≤ 220 mg/day morphine sulfate equivalent) who had general chronic pain [64]. Switching to buprenorphine buccal film from a full μ -opioid receptor agonist at approximately 50% of the dose (a common reduction with opioid rotation) did not increase opioid withdrawal or result in loss of pain control [64]. Although the sample size of this study was small (n = 39), the authors concluded that chronic pain patients treated with full μ -opioid agonists could be switched to buccal buprenorphine film at approximately 50% of the full μ -opioid receptor agonist dose without an increased risk of opioid withdrawal or loss of pain control [64].

Discussion

Efficacy

Buprenorphine buccal film demonstrated efficacy in two 12-week double-blind studies and an additional long-term clinical study [44–46]. Of note, the long-term efficacy of buprenorphine buccal film is supported by reduced pain levels that were generally maintained throughout a 48-week treatment period and were accompanied by low use of rescue medication [45]. These findings support the concept that the classification of buprenorphine as a partial μ -opioid receptor agonist does not translate to partial clinical analgesic efficacy, which is commonly and inaccurately assumed on the basis of receptor activity [65].

In opioid-experienced patients, buprenorphine buccal film had efficacy comparable with that of the extended-release full μ -opioid receptor agonists hydromorphone, hydrocodone and oxycodone, as demonstrated by ≥ 30 and $\geq 50\%$ response rates in similar studies (Table 4) [37,44,66–68]. As a partial μ -opioid receptor agonist, buprenorphine is thus equally effective as full μ -opioid receptor agonists for the treatment of chronic pain; however, head-to-head clinical trials are needed to confirm these comparisons [69].

Clinicians commonly prefer the use of a Schedule IV pain reliever, such as tramadol, because of its scheduling and believe that tramadol and buprenorphine provide similar efficacy. However, clinical data show buprenorphine to be more efficacious than tramadol in providing pain relief [70]. This was confirmed by a clinical study that showed resting pain scores, pain upon movement and rescue analgesia requirements to be significantly lower in patients

Table 4. Response rates across similar studies of opioids.

Chronic pain treatment	Response rate	
	≥30%	≥50%
Buprenorphine buccal film	64	40
Hydromorphone (extended release)	61	42
Hydrocodone (extended release)	68	48
Oxymorphone (extended release)	60	48
Values are listed as percent responders [44,66–68].		

who received transdermal buprenorphine than in those who received oral tramadol [70]. If a clinician prefers to use tramadol on the basis of its Schedule IV classification, the risk/benefit assessment should take into account the possibility that the patient is an ultra-rapid or poor metabolizer of the drug [71]. Ultra-rapid metabolizers have an increased risk for respiratory depression, whereas poor metabolizers commonly experience limited analgesic efficacy [71]. In addition, reported pain reliever misuse has been higher with tramadol than with buprenorphine [72]. Thus, buprenorphine is preferable to tramadol in appropriately selected patients because of expected enhanced efficacy [73].

Safety

In the clinical studies presented here, buprenorphine buccal film was considered to be well tolerated, with no cases of respiratory depression reported [44–46]. Unlike morphine and fentanyl, buprenorphine has a ceiling effect on respiratory depression at higher doses [74,75], which is why respiratory depression is a titration-limiting factor with full μ -opioid receptor agonists [14]. The US Department of Health and Human Services Pain Management Best Practices Inter-Agency Task Force agrees that buprenorphine is safer than full μ -opioid receptor agonists such as morphine, hydrocodone and oxycodone on the basis of this reduced potential for respiratory depression [76]. The unique pharmacodynamic properties of buprenorphine, such as partial agonism at the μ -opioid receptor, may therefore contribute to fewer adverse events compared with full μ -opioid receptor agonists [76,77]. However, head-to-head trials are warranted to make direct comparisons.

A Phase I placebo-controlled study is currently evaluating the dose-dependent effects of buprenorphine buccal film compared with those of oral oxycodone hydrochloride on respiratory function, tolerability and pharmacokinetics in recreational opioid users who are not opioid dependent (ClinicalTrials.gov: NCT03996694) [78]. The results of this pending study will provide insight into the physiological differences in effects on respiratory function between a full μ -opioid receptor agonist and a partial agonist.

Because of potential safety concerns with Schedule II opioids, such as quantity, refill and dosage limits, various federal and state barriers are associated with their prescription [79]. Buprenorphine's Schedule III classification bypasses these issues [79]. A special prescribing waiver is specific to buprenorphine products with indications for medication-assisted treatment for opioid use disorder; a waiver is not required for the transdermal and buccal film formulations because they are indicated for chronic pain and have proven safety and efficacy [37,44–46,50,56,80]. The US Department of Health and Human Services Pain Management Best Practices Inter-Agency Task Force recommendations encourage the primary use of buprenorphine for chronic pain, rather than use only after failure of standard full μ -opioid receptor agonists such as hydrocodone or fentanyl, when clinically indicated [76].

Conclusion

The clinical data presented here support buprenorphine buccal film as a generally well-tolerated treatment option for chronic pain that effectively and continuously reduces pain. The Schedule III classification of buprenorphine by the US Drug Enforcement Administration confirms its enhanced safety profile and reduced abuse potential [77]. As a result, buprenorphine should be considered a first-line treatment for chronic pain in appropriate patients identified by risk/benefit analyses [62]. The increased bioavailability (46–65%) and extended available dose range (75–900 μ g) of buprenorphine buccal film compared with that of the buprenorphine transdermal system support its preferential consideration for chronic pain treatment. These characteristics combined with The US Department of Health and Human Services Pain Management Best Practices Inter-Agency Task Force recommendations support buprenorphine buccal film as a first-line treatment option for chronic pain management at a time when better-tolerated options are needed.

Future perspective

Until new nonopioid analgesics are developed, buprenorphine buccal film represents an effective Schedule III treatment option for chronic pain. We anticipate that buprenorphine buccal film will become the preferred treatment option for chronic pain over other opioids.

Author contributions

All authors directed the content of the manuscript, critically revised the manuscript for scientific accuracy and intellectual content and approved the final manuscript for publication.

Financial & competing interests disclosure

M Hale was a principal investigator for one or more of the clinical trials discussed here and has served on advisory boards for BioDelivery Sciences International, Inc. J Gimbel was a principal investigator for one or more of the clinical trials discussed here. R Rauck has received research funding and has served as a consultant and speaker for BioDelivery Sciences International, Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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- This Department of Health and Human Services guide on the appropriate dosage reduction or discontinuation of long-term opioid analgesics provides advice for clinicians who are contemplating or initiating a reduction in opioid dosage or discontinuation of long-term opioid therapy for chronic pain. It is recommended that patients who are taking high opioid dosages and are unable to taper their current dose despite worsening pain and/or function with opioids should be transitioned to buprenorphine, as buprenorphine has properties that may be helpful in this situation.