Earn CME/CE
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Clinical UPDATE

Buprenorphine in Chronic Pain Management: A New Look at a Familiar Agent

GOAL

The goal of this activity is to improve health-related outcomes by educating clinicians on the use of buprenorphine as an analgesic for the treatment of chronic pain.

LEARNING OBJECTIVES

1. Describe the burden of chronic pain in the United States.
2. Review the efficacy and risks associated with current pharmacologic approaches to the treatment of chronic pain, particularly opioid-related adverse events.
3. Evaluate the role of buprenorphine in the treatment of chronic pain.
4. Compare the safety and efficacy of recently approved and emerging formulations that may improve the administration of buprenorphine.

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INTENDED AUDIENCES

Physicians and other health care providers who manage patients with chronic pain: pain specialists, physiatrists, nurse practitioners, physician assistants, and pharmacists.

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Introduction

Chronic pain is more prevalent than heart disease, diabetes, and cancer combined.[1] In 2016, an estimated 20% of US adults were affected by chronic pain (defined as pain on most days or every day during the prior 6 months), and 8% had high-impact chronic pain (chronic pain that frequently limits life or work activities).[2] These rates reflect a substantial increase in the number of US adults with painful health conditions and severe pain-related interference over the past 2 decades.[3]

Left untreated, chronic pain can lead to a host of adverse outcomes, including depression and anxiety; sleep disturbance and fatigue; reduced quality of life (QoL) and functionality; and restrictions in mobility, employment, and daily activities.[4] The Pain Management Best Practices Inter-Agency Task Force, led by the US Departments of Health and Human Services, Defense, and Veterans Affairs, along with the Office of National Drug Control Policy, described the current state of care for patients with chronic pain as a "crisis" resulting in "profound physical, emotional, and societal costs."[5]

Treatment Landscape

The wide range of nonpharmacologic and pharmacologic treatment modalities for chronic pain presents the clinician with a multidimensional risk–benefit analysis. Drug classes with evidence of benefit for various pain types also carry significant risks. For example, acetaminophen, effective for mild to moderate pain, can cause liver toxicity, especially at high doses; nonsteroidal anti-inflammatory drugs can provide significant relief of pain due to inflammation, but risks include gastrointestinal (GI) issues, renal insufficiency, hypertension, and cardiac-related events; anticonvulsants and musculoskeletal agents can ease pain but are sedating. Conventional opioids, including hydromorphone, hydrocodone, codeine, oxycodone, methadone, morphine, and fentanyl, are among the strongest analgesics on the market; however, as has been well documented, these agents are associated with a host of potential risks.[5]

The unwanted effects of conventional opioids are related to the mechanism of action (MOA) of this drug class. By fully binding to opioid receptors (ORs) in the brain, spinal cord, and other sites, these agents activate both analgesic and reward pathways, leading to risks for misuse and addiction, and can cause respiratory depression, the principal cause of death from overdose. Their MOA also contributes to the development of constipation, sedation, nausea and vomiting, irritability, pruritus, and opioid-induced hyperalgesia. Due to concerns about opioid use disorder (OUD) and its sequelae, clinical guidelines advise that conventional opioids not be used as a first-line treatment for chronic pain.[5,6]

All medications should be selected based on diagnosis, pain mechanisms, and comorbidities after a thorough history, exam, other relevant procedures, and risk–benefit analysis demonstrating that the benefits outweigh the risks.[5]

Buprenorphine Is Different

An often overlooked alternative to conventional opioids is buprenorphine. Derived from the opium alkaloid thebaine of the poppy *Papaver somniferum*, this product is classified as a mixed-action agonist–antagonist. Its MOA is characterized by unique pharmacodynamics that induce potent analgesia with fewer adverse events (AEs) than conventional opioids (Figure 1).[7-9]

Partial Agonist at the μ-OR

Conventional opioids target the μ-OR via 2 distinct downstream signaling pathways: the G-protein pathway, which is responsible for analgesia, and the β-arrestin pathway, which is responsible for side effects such as respiratory depression and lower GI dysfunction. Buprenorphine preferentially activates G-protein signaling without recruiting β-arrestin-2,[10,11] resulting in greater tolerability and a more favorable safety profile than traditional opioids (see *Advantages of Buprenorphine Over Conventional Opioids in Chronic Pain*, page 5). It also facilitates the migration of μ-ORs to cellular membranes, thereby enhancing analgesia by expanding the number of available receptors.[12]

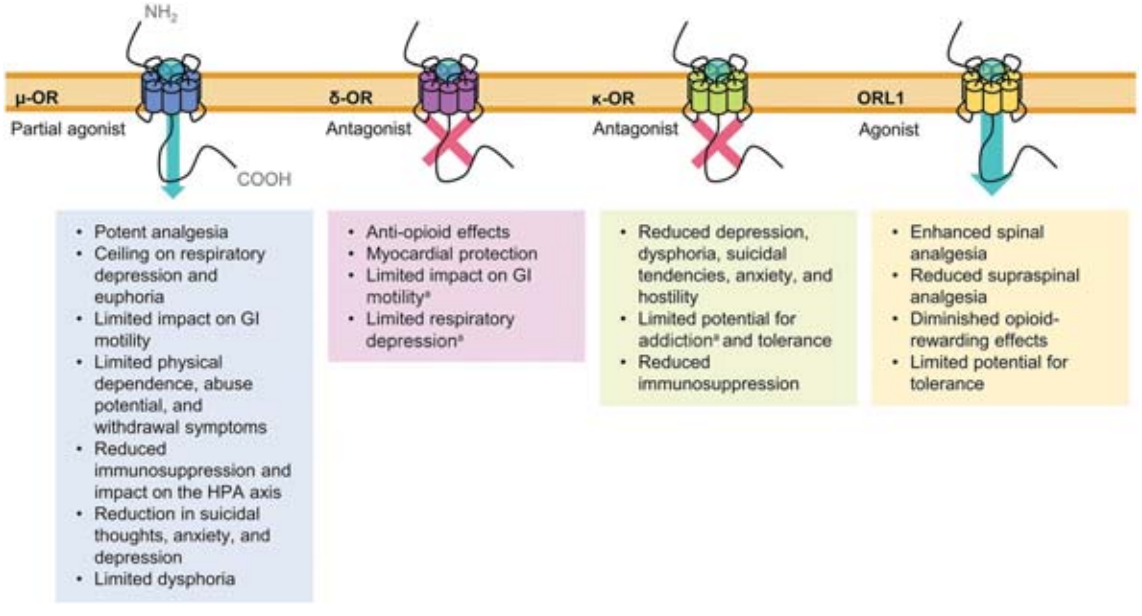

Figure 1. Mechanism of action of buprenorphine.[7]

[a] Predicted effect on the basis of known receptor function.

COOH, carboxyl acid; **GI,** gastrointestinal; **HPA,** hypothalamic–pituitary–adrenal; **OR,** opioid receptor; **ORL,** opioid receptor-like.

In addition, buprenorphine dissociates more slowly from the μ-OR than traditional opioids, resulting in a prolonged duration of analgesia and a lower potential for withdrawal upon termination of therapy.[7] Finally, buprenorphine has high affinity for the μ-OR, resulting in tight binding and conferring competitive inhibition against full μ-receptor agonists. Thus, if a patient taking buprenorphine also takes a full opioid, the buprenorphine will prohibit it from reaching the receptors and producing euphoric effects. This mechanism is the basis for the use of buprenorphine in OUD.[7]

Full Antagonist at the δ- and κ-ORs

Antagonism of δ-OR and κ-OR makes buprenorphine less likely than conventional opioids to induce sedation, dysphoria, constipation, and hyperalgesia; and may potentiate antidepressant and anxiolytic effects.[15-17]

Partial Agonist at the Human OR-Like Receptor

The agonist effect of buprenorphine on the OR-like (ORL)-1 receptor blocks the brain reward system. This slows the development of tolerance to analgesic effects, resulting in a lower potential for misuse than conventional opioids.[16] It also may contribute to analgesic efficacy via activation of ORL-1 receptors in the the spinal cord.[17]

Tissue Specificity

Buprenorphine preferentially activates spinal vs supraspinal μ-ORs, providing analgesia while limiting the development of euphoria and respiratory depression.[7]

Misconceptions About Buprenorphine

Because buprenorphine is a partial μ-OR agonist, it has been misconstrued to exhibit only partial analgesic efficacy compared with full μ-OR agonists.[16,18] A partial agonist is defined as "a compound with an intermediate intrinsic activity that at full receptor saturation produces less than the maximal effect obtainable."[18] Buprenorphine was classified as a partial agonist based on in vitro assays; however, in clinical studies for various conditions including surgical pain, acute renal colic pain, and chronic cancer and noncancer pain, buprenorphine has demonstrated analgesic and antihyperalgesic efficacies equal or superior to agents considered to be full μ-OR agonists, including morphine, fentanyl, sufentanil, and oxycodone.[18-20] Buprenorphine is 25 to 100 times more potent than morphine.[14]

Other misconceptions concern the pharmacology and indications for buprenorphine. Although buprenorphine is better known for its role in treating OUD, the original impetus for its development was the need for an effective analgesic with a high margin of safety and low abuse potential.[21] Before buprenorphine was approved for OUD in 2002, it was used in Europe for many years in both injectable and sublingual formulations for moderate to severe pain.[22,23] Doses of buprenorphine approved for OUD are considerably higher than those used for pain management; however, this does not imply that doses for chronic pain lack analgesic potency.[18]

Finally, some prescribers consider using buprenorphine only after the failure of conventional opioids. In its 2019 publication, the interagency task force advocated for more widespread use of buprenorphine in chronic pain—particularly as primary therapy *before* initiating conventional opioids.[5] In its guidance, the group emphasized that buprenorphine may be more tolerable than conventional opioids and less likely to cause respiratory depression.[24]

Scheduling

Conventional opioids are typically classified as Schedule II controlled substances, meaning that they have a high potential for abuse and their use can lead to severe psychological or physical dependence. Buprenorphine is classified as a Schedule III controlled substance, meaning that it has moderate to low potential for physical and psychological dependence.[25] This status serves to reassure prescribers about the relative safety of buprenorphine as well as reduce the difficulties associated with both prescribing and filling prescriptions for opioid analgesics. For example, orders for Schedule III drugs can be telephoned into a pharmacy and can be refilled, whereas those for Schedule II drugs cannot.[26] In addition, some states restrict prescribing of Schedule II drugs by mid-level providers such as nurse practitioners (NPs) and physician assistants (PAs; Figure 2), impose limits on the number of doses or applicable diagnoses, or require specialized education or documentation.[27]

- Georgia, Oklahoma, and West Virginia prohibit NPs from prescribing any Schedule II drugs
- Georgia, Kentucky, and West Virginia prohibit PAs from prescribing any Schedule II drugs
- Arkansas and Missouri limit both NPs and PAs to prescribing hydrocodone products only
- Louisiana allows NPs allows to prescribe Schedule II drugs only for patients with attention-deficit/hyperactivity disorder
- Texas allows NPs and PAs to prescribe Schedule II drugs only for inpatients
- Hawaii allows PAs to prescribe Schedule II drugs only for inpatients

Formulations of Buprenorphine

Two formulations of buprenorphine are FDA-approved for chronic pain: buccal and transdermal (Table 1).[28,29] The development of these and other nonoral modes of delivery was necessitated by the fact that buprenorphine undergoes presystemic metabolism in the GI tract and extensive first-pass metabolism when ingested orally. Orally ingested buprenorphine has a bioavailability of only 15%, which is insufficient for pain management.[14,30,31] However, due to its highly lipophilic structure and low molecular weight, buprenorphine has high systemic bioavailability when delivered transdermally or via the oral mucous membrane.[32]

Transdermal Buprenorphine

Transdermal buprenorphine is indicated for the management of pain severe enough to require daily, around-the-clock (ATC), long-term opioid treatment for which alternative treatment options are inadequate.[29] This language, also used in the labeling for buprenorphine buccal film, is mandated by the FDA for use in the labels of all extended-release (ER) or long-acting opioids indicated for chronic pain.[33] In the transdermal formulation of buprenorphine, the active agent is embedded in an adhesive polymer matrix that controls the rate of drug delivery and produces stable plasma concentrations with limited fluctuation over 7 days.[17,19,34,35]

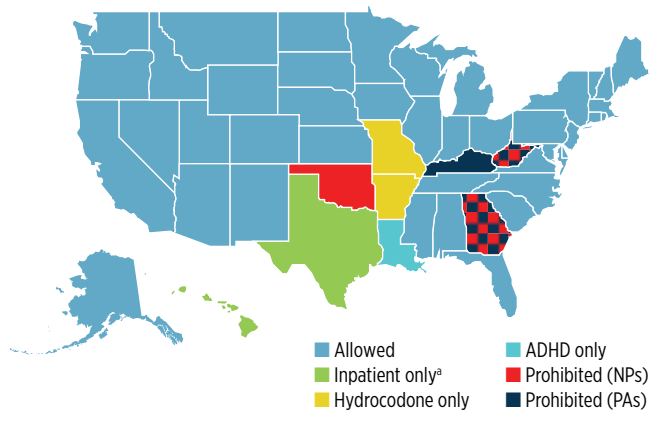

Figure 2. Prescribing of Schedule II drugs by NPs and PAs in the United States.[27]

[a] Hawaii, PAs; Texas, NPs and PAs.

ADHD, attention-deficit/hyperactivity disorder; **NP,** nurse practitioner; **PA,** physician assistant.

Transdermal buprenorphine is suitable for patients receiving ≤80 oral morphine milligram equivalents (MME) per day. It may not produce adequate analgesia in patients who require >80 MME daily.[29] Five strengths are approved by the FDA: 5, 7.5, 10, 15, and 20 μg per hour. Each patch is designed to be worn for 7 days.[29] Although transdermal buprenorphine is available in European countries in 35-, 52.5-, and 70-μg-per-hour patches, US dosing is capped at 20 μg per hour due to concerns about QT prolongation.[12] A study cited in the prescribing information found that doses of 40 μg per hour resulted in a maximum mean QT prolongation of up to 9.2 milliseconds across assessment time points.[28] This increase is well below the level considered likely to be associated with proarrhythmic effects.[36] An analysis of FDA and World Health Organization (WHO) postmarketing surveillance data did not identify any signal of increased risk for cardiac arrhythmia for transdermal buprenorphine formulations available in the United States at unit strengths from 5 to 20 μg per hour and outside the United States at unit strengths from 35 to 70 μg per hour.[37]

The clinical development program for transdermal buprenorphine comprised four 12-week, double-blind, controlled clinical trials in patients with moderate to severe chronic low back pain (CLBP; 3 studies) or osteoarthritis (OA; 1 study) using pain scores as the primary efficacy variable. Efficacy was demonstrated in 2 of the low back pain trials.[38,39]

Study 1 enrolled 1,024 opioid-naive patients with CLBP and suboptimal responses to nonopioid therapy.[38] After an open-label dose titration period, 53% of patients receiving transdermal buprenorphine were able to titrate to a dose that was tolerable and that induced adequate analgesia. These patients were then randomly assigned to continued treatment with their titrated or placebo dose for 12 weeks. Transdermal buprenorphine was associated with statistically lower average pain scores over the previous 24 hours.

Study 2 enrolled 1,160 patients receiving conventional opioid therapy for CLBP. After tapering off their opioid regimens, 57% of patients were able to titrate to and tolerate transdermal buprenorphine at 20 μg per hour.[39] They were then randomized to continue with the 20-μg-per-hour patch or receive a low control dose of 5 μg per hour. At week 12, patients who received 20 μg per hour had lower average pain scores over the previous 24 hours compared with those who received the control dose. In addition, a reduction in pain scores of ≥30% was demonstrated in 49% of patients who received the higher dose vs 33% of those who received the control dose. The 2 other studies in the clinical development program did not demonstrate efficacy.[29]

In other studies, transdermal buprenorphine was superior to placebo in noncancer pain,[40] low back pain,[41,42] and pain from OA[43]; noninferior to tramadol tablets,[44] a codeine/acetaminophen combination,[45] and sublingual buprenorphine[46] in OA pain; and associated with improved QoL in patients with CLBP.[47]

Buprenorphine Buccal Film

Buprenorphine buccal film is indicated for the management of pain severe enough to require daily, ATC, long-term opioid treatment, and for which alternative options are inadequate. The product consists of buprenorphine that has been incorporated into a flexible, water-soluble mucoadhesive polymeric film, which is applied to the inner lining of the cheek. The film erodes in a matter of minutes, efficiently delivering buprenorphine across the buccal mucosa.[28]

Suitable for patients with a prior daily opioid requirement (before taper) ≤160 MME, buprenorphine buccal film is the most appropriate buprenorphine formulation for patients whose daily requirements exceed 80 MME, a level at which transdermal buprenorphine may not provide adequate analgesia.[28,29] It is available in 7 dose strengths: 75, 150, 300, 450, 600, 750, and 900 μg, and steady-state conditions were reached within 3 days of dosing.[31,48] Compared with transdermal buprenorphine, the buccal film produces therapeutic plasma concentrations across a wider range of doses in a shorter period and provides greater titration flexibility.[31]

The efficacy of buprenorphine buccal film was evaluated in three 12-week, double-blind, placebo-controlled, enriched-enrollment clinical trials in patients with moderate to severe CLBP. The primary efficacy variable was changed in mean daily pain intensity scores from baseline to week 12. Efficacy for buprenorphine buccal film was demonstrated in 2 of the trials.

Table 1. Formulations of Buprenorphine[28,29]

		Buprenorphine Buccal Film[28]	Buprenorphine Transdermal System[29]
		Belbuca (BioDelivery Sciences International, Inc)	Butrans (Purdue Pharma, LP)
Initial US approval		2015	2010
Indication		Management of pain severe enough to require daily, ATC, long-term opioid treatment and for which alternative treatment options are inadequate	
Dosage forms		75, 150, 300, 450, 600, 750, and 900 μg	5, 7.5, 10, 15, and 20 μg/h
Initial dosing	Opioid-naive	75 μg qd or q12h	5 μg/h (7-d patch)
	Conversion from other opioids	• Taper previous opioid to ≤30 MME • 75 μg qd or q12h for pts on <30 MME • 150 μg q12h for pts on 30-89 MME • 75 μg q12h for pts on 90-160 MME[a]	• Discontinue all ATC opioids • 5 μg/h for pts on <30 MME • 10 μg/h for pts on 30-80 MME
Dosage adjustment		150-μg/12-h increments q≥4d	5-, 7.5-, or 10-μg/h increments q≥3d
Steady-state, h		72	72
Bioavailability relative to IV, %		65	15
Terminal half-life, h		27.62±11.2	26
Application		Inside of cheek, yellow side down, until fully dissolved	Upper outer arm, upper chest, upper back, or side of chest

[a] Patients taking >160 MME should consider an alternative analgesic.

ATC, around-the-clock; **IV,** intravenous; **pts,** patients; **MME,** morphine milligram equivalent.

The first study enrolled 749 opioid-naive patients.[49] During an open-label dose-titration period lasting ≤6 weeks, patients were titrated to a dose of buprenorphine buccal film in the range of 150 to 450 μg until adequate analgesia and tolerability were achieved for a minimum of 14 days. Of the patients who entered the open-label dose-titration period, 61% achieved that goal and were randomized to continue their titrated dose or matching buccal placebo. At the end of the 12-week, double-blind treatment period, a higher proportion of patients who received buprenorphine buccal film had ≥30% reduction in pain score (62%) compared with those who received placebo (47%). Buprenorphine buccal film also was associated with ≥50% reduction in pain score in more patients than placebo (41% vs 33%, respectively).[49]

For the second study, 810 patients receiving ATC opioid analgesics had their prior opioids tapered to 30 MME per day and then entered an open-label, dose-titration period with buprenorphine buccal film for ≤8 weeks.[50] Doses of buprenorphine buccal film were 150 μg every 12 hours for those on 30 to 89 MME per day and 300 μg every 12 hours for those on 90 to 160 MME per day before taper. The dose was increased in increments of 150 μg every 12 hours after 4 to 8 days for ≤6 weeks until adequate analgesia that was generally well tolerated was achieved for 14 days. Of the patients who entered the open-label titration period, 63% were able to titrate to a tolerable and effective dose and were randomized to either continue their titrated dose or receive a placebo buccal film for a 12-week double-blind period. Results showed that a higher proportion of patients who received buprenorphine buccal film had ≥30% reduction in pain score from baseline to week 12 than those who received placebo (64% vs 31%, respectively), and a higher proportion of patients who received buprenorphine buccal film also had ≥50% reduction in pain score at the end of the study compared with those who received a placebo (39% vs 17%, respectively). Buprenorphine buccal film was generally well tolerated and associated with a low occurrence of AEs typically associated with opioids (nausea, constipation, vomiting, headache, dizziness, and somnolence).[50]

In an open-label study designed to evaluate long-term safety and tolerability, buprenorphine buccal film demonstrated sustained efficacy and good tolerability throughout a 48-week evaluation period.[51] The need for rescue medication declined significantly from baseline during that period as well.

Systematic Reviews

In a systematic review of 25 randomized controlled clinical studies that investigated the efficacy of different buprenorphine formulations (intravenous [IV], sublingual with and without naloxone, buccal, and transdermal) in patients with chronic pain, 14 studies evinced an association between buprenorphine and improved pain scores.[52] Fifteen trials investigated transdermal buprenorphine for the treatment of a wide range of pain disorders; 10 of these trials showed significant improvement in pain for transdermal buprenorphine vs a comparator. Similar results were demonstrated for 1 of 6 studies of sublingual and IV buprenorphine and 2 of 3 studies of buccal buprenorphine.

Finally, a 2019 systemic review of 33 clinical studies confirmed the efficacy, safety, and tolerability of buprenorphine for pain relief at doses ranging from 5 to 140 μg per hour.[15] It included 29 studies on transdermal buprenorphine and 4 on buprenorphine buccal film and involved patients with CLBP, OA- and cancer-related pain, and musculoskeletal pain for durations ranging from 6 days to 5.7 years. In addition to pain relief, the benefits of buprenorphine treatment included improvements in general QoL, sleep duration, vitality, and mental health; reduced need for breakthrough analgesia; efficacy in patients >65 years of age, and overall good tolerability. The most commonly reported AEs were nausea, headache, application-site pruritus, dizziness, constipation, somnolence, vomiting, dry mouth, and application-site reactions.

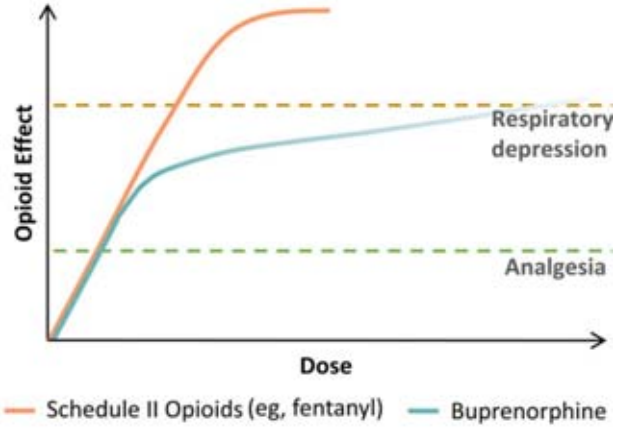

Figure 3. Ceiling effect for respiratory depression with buprenorphine.[18]

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Advantages of Buprenorphine Over Conventional Opioids in Chronic Pain

Buprenorphine has several advantages over conventional opioids (Table 2).

Respiratory Depression

Respiratory depression, characterized by increased arterial pressure of carbon dioxide, reduced arterial pressure of oxygen, and hypoxia, is a serious AE that represents a major limiting factor in the provision of adequate analgesia.[23] When prescribing conventional opioids, clinicians are challenged to maintain the delicate balance between the need to provide optimal pain relief and the need to avoid respiratory depression and its potentially life-threatening consequences. The risks associated with respiratory depression are especially pronounced in opioid-treated patients with respiratory conditions such as obstructive sleep apnea. Although the incidence of respiratory depression in patients receiving prolonged opioid therapy for chronic pain is unknown, opioid-induced respiratory depression requiring rescue occurs in approximately 0.5% of patients in the postoperative period.[53]

With conventional opioids, increases in both analgesia and the risk for respiratory depression are dose-dependent (Figure 3).[18] An increased risk for respiratory depression accompanies dose-related increases in analgesia.[54] Consequently, the ceiling (the apparent maximum effect regardless of drug dose) for respiratory depression is paralleled by limited analgesic efficacy.[55] Buprenorphine is unique in that it demonstrates a ceiling for respiratory depression but not for analgesia.

Table 2. Benefits of Buprenorphine vs Full Agonist Opioids

Ceiling effect on respiratory depression
Can be used in patients with renal impairment
Less risk for fracture
Effective for multiple pain types (including neuropathic and cancer pain)
Less risk for constipation
Lower abuse potential
Prolonged duration of analgesic effect
Lower potential for withdrawal upon termination of therapy
Fewer prescription restrictions due to Schedule III status
Not immunosuppressive

This characteristic was demonstrated in a group of healthy volunteers who were administered 2 weight-adjusted IV doses of buprenorphine (0.2 and 0.4 mg/70 kg).[56] Pain was then induced by transcutaneous electrical stimulation with a gradually increasing current. Although the peak analgesic effect of buprenorphine increased significantly with the doubled dose, respiratory depression remained similar in both magnitude and timing for the 2 doses tested.

In a double-blinded placebo-controlled study comparing respiratory depression in patients administered buprenorphine or fentanyl, fentanyl was associated with a dose-dependent reduction of minute ventilation with respiratory instability at doses of ≥2.9 μg/kg.[55] Buprenorphine was likewise associated with dose-dependent reduction in minute ventilation, but a leveling-off at approximately 50% of baseline respiration rate was observed at dosages of ≥3 μg/kg.

In contrast to those results, a systematic review that aimed to characterize the analgesic efficacy and AEs of buprenorphine compared with morphine for acute pain, demonstrated that both drugs were associated with similar rates of respiratory depression and sedation.[57]

Should respiratory depression occur with buprenorphine use, it can be reversed by the continuous infusion (rather than bolus administration) of high-dose naloxone.[23,59] Coadministration of buprenorphine with other opioids, general anesthetics, various sedatives and hypnotics (including benzodiazepines), antihistamines, and other central nervous system (CNS) depressive medications carries a significant and potentially lethal risk for respiratory depression and should be avoided.[16,32]

Immunosuppression

Alterations in immune responses have been reported as a potential side effect of opioids. These aberrant responses are proposed to result from the downregulation of innate and acquired immune pathways. Opioid-induced immunosuppression primarily has been observed in in vitro and animal models, and its clinical significance in humans is uncertain. Nonetheless, laboratory findings of opioid-induced immunosuppression are of potential concern because of the possibility that the immunologic effects of opioids may increase susceptibility to infection and affect disease processes and outcomes of surgeries or pharmacotherapy.[59] Opioids vary in their potential to affect the immune system; studies have shown that the risk for opioid-induced immunosuppression is highest with morphine, moderate with fentanyl, and negligible with tramadol or buprenorphine.[60] In an animal study designed to investigate the differential effects of buprenorphine and morphine on immune and neuroendocrine functions, buprenorphine, in contrast to morphine, did not activate the hypothalamic–pituitary access and was not associated with immunosuppression.[61]

The lack of effect on immune function with buprenorphine has been ascribed to the drug's chemical properties and MOA, including antagonism at the κ-OR.[62]

Constipation

Opioid-induced constipation (OIC) is a common AE that can occur with the long-term use of opioids, including buprenorphine. It affects approximately 40% of patients taking opioids.[63] In a systematic review of AEs associated with transdermal buprenorphine vs transdermal fentanyl in patients with chronic pain, the incidence of constipation ranged from 1% to 19.5% for buprenorphine and 3.1% to 45% for fentanyl. Although direct head-to-head comparisons from high-quality studies of the 2 agents are not available, evidence from low-quality studies suggests that constipation occurs less often with transdermal buprenorphine than with transdermal fentanyl, and that both agents are associated with higher rates of constipation than sustained-release morphine at equivalent doses.[64]

Buprenorphine may be less likely to cause constipation than other opioids because it does not appear to cause spasm in the sphincter of Oddi.[17] According to a clinical guideline for the management of OIC and bowel dysfunction, transdermal buprenorphine may be advantageous in avoiding OIC due to its provision of a uniform blood opioid level with fewer peaks in serum concentration.[65]

Special Patient Populations

Cancer

Pain is associated with serious adverse effects on QoL in patients with cancer. A 2016 review showed that cancer pain was prevalent in 39% of patients after curative treatment; 55% during anticancer treatment; and 66% in advanced, metastatic, or terminal cancer.[66] More than one-third of patients rated their cancer-related pain as moderate or severe, suggesting a need for improved management approaches.

Various case series, prospective uncontrolled studies, and randomized trials have demonstrated the efficacy of buprenorphine in cancer-related pain.[67] In guidelines from the European Association for Palliative Care on the use of opioids for the treatment of cancer pain, transdermal buprenorphine is recommended as an effective, noninvasive means of opioid delivery in patients who cannot swallow. It is also useful in patients who do not tolerate oral medications due to chemotherapy-associated nausea and vomiting.[68] In a systematic review that examined the use of transdermal buprenorphine, fentanyl patches, or a combination of both in cancer pain, the 2 therapies were found to be similarly safe and efficacious. However, buprenorphine was associated with a lower risk for analgesic tolerance and better overall tolerability.[69] A Phase 4 multicenter clinical trial demonstrated transdermal buprenorphine to be as efficacious in treating chronic cancer pain as the Schedule II opioids morphine, oxycodone, and fentanyl.[70]

Neuropathic Pain

Traditional opioid agonists are regarded as less effective for neuropathic pain than for other pain conditions, despite their frequent use for that purpose. A Cochrane review found "insufficient evidence to support or refute the suggestion that buprenorphine has any efficacy in any neuropathic pain condition." This conclusion was reached due to a lack of clinical trials studying buprenorphine for this use.[71] Nonetheless, the benefits of buprenorphine have been demonstrated in case studies, open-label studies, and postmarketing studies involving neuropathic pain conditions such as neuropathy caused by traumatic amputation, central neuropathic pain, HIV-related neuropathy, neuropathic pain associated with dynamic and mechanical allodynia, and chronic painful neuropathies of various etiologies.[72-77] These positive results are consistent with animal and human experimental studies demonstrating that buprenorphine dampens central sensitization.[78] Evaluations in laboratory animals using pain assays such as the formalin test, cold tail-flick test, and diffuse noxious inhibitory control test provide evidence that buprenorphine may possess analgesic mechanisms in neuropathic pain that are distinct from those operating in conventional opioids,[79] including differences in signal transduction.[32] Members of a consensus panel on opioids and the management of chronic severe pain in older adults concluded that buprenorphine "shows a distinct benefit in improving neuropathic pain symptoms."[80]

Older Adults

Pain becomes more common with advancing age even as treatment options narrow, due to risks for adverse drug effects. Older adults are vulnerable to these risks because they have higher rates of polypharmacy and comorbidities, slower metabolisms, and age-related pharmacokinetic (PK) and pharmacodynamic changes. These can include alterations in the onset of action, rate of elimination, and half-life of drugs.[81]

Several studies have demonstrated the suitability of buprenorphine for this patient population. Because it is highly bound to the globulin fraction of plasma proteins, buprenorphine has a reduced risk for interactions with other drugs.[82] In a study investigating the PK of buprenorphine transdermal patches in healthy volunteers aged ≥75 and 50 to 60 years, average buprenorphine exposure at steady state was only slightly lower for the ≥75 arm.[81] Transdermal buprenorphine has

demonstrated similar and sometimes higher analgesic efficacy in patients >65 years of age compared with younger patients.[83]

With advancing age, individuals become more vulnerable to fractures and their complications.[84] A nationwide population-based study from Denmark showed that although morphine and several other conventional opioids were associated with an increased risk for fractures, buprenorphine was not.[85] The authors noted that the increased risk for fractures was likely due to drug-related CNS effects such as dizziness. A recent retrospective analysis that compared the safety of transdermal buprenorphine in 2 age groups found a similar incidence of AEs in patients >65 years (range, 65-98 years) and those <65 (range, 18-64). However, constipation, peripheral edema, and urinary tract infection occurred more often in the older age group. Moreover, the authors found a statistically significant treatment-by-age interaction for arthralgia, localized and nonapplication site-related rash, falls, accidents, and injuries. As with other opioids, the potential benefits of transdermal buprenorphine need to be balanced against the potential risks, particularly in older adults.[83]

Impaired Renal Function

When prescribing conventional opioids to patients with impaired renal function, the risk for toxicity secondary to the accumulation of active metabolites usually requires monitoring of creatinine clearance as well as reductions in the number and size of doses.[80] These measures are not required when prescribing buprenorphine to patients with renal dysfunction, as this agent is primarily eliminated by the liver. Because buprenorphine and its metabolites do not accumulate in patients with renal dysfunction, it can be used even in patients with dialysis-dependent renal failure or those who have discontinued dialysis.[16,80,87] In an independent study referenced in the package insert for buccal buprenorphine, plasma buprenorphine concentrations after IV bolus and continuous IV infusion were comparable regardless of renal function.[29]

Conclusion

A growing number of individuals in the United States are affected by chronic pain and its effects on functional status, psychosocial well-being, and QoL. Conventional opioid analgesics have a well-established role in chronic pain, but their use is limited by side effects, insufficient efficacy in certain pain types, and the potential for misuse and overdose. Both transdermal buprenorphine and buprenorphine buccal film are increasingly recognized as well-tolerated, efficacious alternatives with distinct advantages in certain populations and clinical scenarios. Continued study of the mechanisms, efficacy, and safety of buprenorphine will help clinicians select appropriate treatments for managing chronic pain.

Case Study: Conversion to Buprenorphine From a Conventional μ-OR Agonist

Presentation

Rupert is a 67-year-old retired construction worker who is new to the practice. His chief complaint is CLBP of 4 years' duration, and his medical history includes type 2 diabetes mellitus diagnosed about 2 years ago. He has no significant surgical history. Rupert has been stable, with minimal pain and good function, on a daily dose of 60 mg of oxycodone ER (90 MME/day) for 2 years. During the past few months, Rupert has noticed increased pain that prevents him from completing yard work and household chores. He rates the intensity of his pain as 4 to 5 on a 0- to 10-point visual analog scale, with periodic increases related to physical tasks.

Discussion

Rupert is a good candidate for conversion to buprenorphine buccal film. Given that his present opioid dose exceeds 80 MME per day, transdermal buprenorphine may not provide adequate analgesia.[28,29] According to an expert panel convened to advise on the clinical use of buprenorphine in chronic pain (including conversion strategies for conversion from a full μ-OR agonist), a switch to buprenorphine should be considered under the following circumstances[18]:

1. Lack of efficacy, including tolerance or hyperalgesia
2. Analgesia or anticipated improved risk–benefit vs current therapy
3. Concern from health care providers regarding prescription of a Schedule II opioid due to risk for addiction, misuse, or overdose death
4. Limited ability to use oral formulations, as in patients with altered GI motility or function (eg, after bariatric surgery)
5. Decision to change from an immediate-release to a longer-acting analgesic with a relatively favorable safety profile and Schedule III classification

Rupert meets the first 3 criteria:

1. He is experiencing inadequate analgesia with his current regimen; given that low back pain frequently includes a neuropathic component, buprenorphine may provide better pain relief than conventional opioids[80]
2. Diabetes and advancing age can place him at risk for reduced renal clearance of oxycodone and its metabolites, resulting in a suboptimal risk–benefit ratio for continued oxycodone use; buprenorphine is metabolized by the liver and is safe for patients with reduced renal function[87]
3. Guidelines from the Centers for Disease Control and Prevention recommend against increasing dosages beyond 90 MME per day due to the risk for potential AEs including drug overdose/misuse; buprenorphine buccal film is a safer Schedule III alternative that has the potential to improve pain control at a lower dose[6]

The prescribing information for buprenorphine buccal film states that before initiating therapy in an opioid-experienced patient, the current daily opioid dose should be tapered to no more than 30 MME to reduce the risk for opioid withdrawal.[28] Short-acting opioids are allowed during titration periods. For patients taking between 90 and 160 MME, therapy should be initiated with 300 μg buprenorphine buccal film every 12 hours after analgesic taper. The label further advises that the medication should be titrated to a dose that provides the patient with adequate analgesia and minimizes AEs, with a maximum dose of 900 μg every 12 hours. Based on current literature, member expertise, and a group discussion, the expert panel concluded that this conversion strategy is impractical and may precipitate withdrawal.[18] Rather, the panel advised direct conversion to buprenorphine with no weaning period. Instructions for patients converting from other opioid agonists at varying doses to transdermal buprenorphine are available in the consensus statement.

The following process, for patients taking oxycodone doses of ≥60 mg per day, would be used for Rupert:

1. Discontinue the current opioid after the last nighttime dose
2. Consider initiating an adrenergic α2 agonist (eg, clonidine, lofexidine) or an immediate-release formulation of the current opioid to reduce the risk for withdrawal
3. Initiate buprenorphine the following morning per the prescribing information, as either 10-μg per hour transdermal buprenorphine or 150-μg buccal buprenorphine twice daily, and titrate as needed for pain per recommendations in the prescribing information

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