# Buprenorphine: A unique opioid with broad clinical applications

Nalini Vadivelu, MD
Roberta L. Hines, MD

## ABSTRACT

*The analgesic potential of buprenorphine, a high-affinity partial μ agonist, has been a subject of study for several decades. The drug is now widely recognized as being extremely effective in relieving perioperative pain, with little of the addictive potential or risk associated with pure μ agonists. Studies have suggested that buprenorphine produces adequate analgesia via almost any route of administration, including transdermal and subcutaneous. It has also been used, with positive results, in the treatment of opioid addiction, and potential remains for research into other roles, e.g., as an anti-inflammatory agent or an antihyperalgesic medication.*

*Key words: buprenorphine, opioid, μ agonist, analgesia, perioperative pain, route of administration, addiction, withdrawal, detoxification*

## INTRODUCTION

Buprenorphine is a semisynthetic oripavine alkaloid derived from thebaine. It is a long-acting, lipid-soluble, mixed agonist-antagonist opioid analgesic, first synthesized in 1966. Continued interest in buprenorphine has been attributed to its unique pharmacological effects, being a partial μ agonist with moderate intrinsic activity and with high affinity to and slow dissociation from μ opioid receptors.[1,2] Buprenorphine was one of the first narcotic analgesics to be studied for its abuse liability in humans. The low abuse liability of the drug soon led to its widespread use as a therapeutic agent in patients with opioid dependence. At the present time, the principal clinical application of buprenorphine is as an analgesic for moderate to severe pain in the perioperative setting and in the treatment of heroin addiction.[3] This article focuses on its use in the perioperative setting. Recent clinical interest in the possible usefulness of buprenorphine in the treatment of pain states dominated by central sensitization is also discussed.

## PHARMACOLOGY AND PHARMACOKINETICS

Buprenorphine was initially classified as either a mixed agonist-antagonist analgesic or a narcotic-antagonist analgesic.[4] In most preclinical antinociceptive tests, buprenorphine was shown to be fully efficacious, with an antinociceptive potency 20 to 70 times higher than that of morphine.[5,6] There are controversial reports on naloxone's ability to reverse antinociception produced by buprenorphine. In some studies, buprenorphine-induced analgesia exhibited a lack of naloxone reversibility.[7] However, Schmauss et al.[8] have reported a reversal of buprenorphine-induced antinociception using naloxone. They explained it as the result of the existence of three discernable populations of opioid receptors in the spinal cord, the activations of which have different effects on a subject's response to noxious stimuli. Buprenorphine exhibits a longer duration of action and decreased withdrawal symptoms compared with pure μ agonists such as heroin.[9]

The analgesic effect of buprenorphine appears to depend upon the integrity of descending fibers from the rostral ventromedial medulla. Just as with morphine, the descending fibers are critically important to the analgesic effect of the opioid, regardless of the type of noxious stimulation eliciting pain. Residual analgesic effects of opioids after inactivation of descending fibers may be due to peripheral effects in the presence of inflammation.[10]

Buprenorphine used in therapeutic concentrations in humans does not appear to cause clinically significant interactions with other cytochrome P–metabolized drugs.[11] However, its pharmacology is complicated by the presence of an active N-dealkylated metabolite of buprenorphine, norbuprenorphine.[12] A study involving the intraventricular administration of buprenorphine and norbuprenorphine in rats suggested that the intrinsic analgesic activity of norbuprenorphine was one-fourth that of buprenorphine. It is possible that the remarkably weak pharmacological effect of norbuprenorphine after intraventricular administration may be due not only to the low ability of norbuprenorphine to permeate the blood-brain barrier but also to its small intrinsic pharmacological profile.[13] The neurotoxic effects of norbuprenorphine are not known.

Buprenorphine's affinity for μ opioid receptors allows

pharmacologically effective occupancy at low plasma concentrations, with an analgesic effect being measurable at 5 to 10 percent receptor occupancy. The parenteral formulation of buprenorphine has a speed of onset of five to 15 minutes following either intravenous (IV) or intramuscular (IM) administration. Onset of analgesia occurs in 15 to 45 minutes with sublingual buprenorphine.

Buprenorphine is metabolized by the gut and liver. In humans, the majority of any dose administered by any route is excreted via the gastrointestinal tract. Following administration and independent of route, some 15 percent of the original dose is excreted in the urine. In short-term treatment with buprenorphine, end-stage renal failure does not seem to affect the excretion of the drug. In chronic therapy, measurements of plasma levels of buprenorphine and its metabolites in patients with and without renal failure showed that levels of the metabolites were increased in the patients with renal failure, while buprenorphine levels were similar in both groups. This supports a biliary excretion route for buprenorphine but points to the importance of the renal excretion route for the metabolites.[11]

## RELATION BETWEEN PHARMACOLOGY AND CLINICAL EFFECTS

Buprenorphine interacts with μ, κ, and δ opioid receptors and exhibits a slow dissociation from μ receptors.[14] These are the three major types of opioid receptors seen in large concentrations in the substantia gelatinosa of the spinal cord, a region that is a major site for early integration of nociceptive input.[15]

### μ and κ receptors

Because of its properties regarding μ and κ receptors, buprenorphine can be used both as an analgesic agent and in the treatment of opioid abuse. Buprenorphine is a mixed agonist-antagonist drug exhibiting partial agonist activity toward μ opioid receptors and antagonist action at κ opioid receptors.[7] As a result of its partial agonist activity at μ opioid receptors and its long half-life, buprenorphine has proven to be an excellent alternative to methadone for either maintenance therapy or detoxification of the opioid addict.[12] At μ receptors, buprenorphine has high affinity and intermediate intrinsic efficacy, as measured by both in vitro functional assays and in vivo behavioral assays. Buprenorphine exhibits slow dissociation from μ opioid receptors. Buprenorphine, morphine, heroin, and methadone all show different patterns of G protein activation in evoking μ-opioid-receptor-mediated supraspinal antinociception.[16] Some studies have suggested that buprenorphine may have an agonistic activity at κ opioid receptors as well.[17]

### δ receptors

Compared with the well-characterized effects of buprenorphine at μ and κ opioid receptors, little is known about its activity at δ receptors. In vitro studies suggest that buprenorphine could produce δ-receptor-mediated antagonist or agonist effects in vivo, either directly or through its metabolites. The relative potency of buprenorphine in producing δ-receptor-mediated effects in vivo is largely unknown. In rhesus monkeys, δ antagonist effects occurred with buprenorphine doses approximately 30-fold higher than those producing μ- or κ-receptor-mediated effects. Thus, buprenorphine was less capable of producing δ-receptor-mediated effects than either μ- or κ-receptor-mediated effects.[18] In other research, though, buprenorphine has been shown to have an affinity for the δ opioid receptor and may have clinical utility for delayed, receptor-mediated myocardial protection.[19]

### New receptors

The nociceptin/orphanin FQ (N/OFQ) receptor has been shown to be pharmacologically distinct from the classic opioid receptors. N/OFQ is an endogenous ligand for the human opioid-receptor-like receptor (ORL-1). Buprenorphine was recently identified as a full ORL-1 agonist using a reporter-gene assay. The N/OFQ agonism of buprenorphine might contribute to the actions of buprenorphine in pain models in vivo separately from its μ- or κ-receptor-mediated effects.[20] The question of whether the ORL-1 component might be involved in antinociception, or rather pronociceptive/antiopioid activities, for buprenorphine will likely not be answered until selective ORL-1-antagonist compounds are available.

## CLINICAL TRIALS AND APPLICATION IN CLINICAL PAIN MANAGEMENT

Buprenorphine can be administered via multiple routes for pain management in humans. A vast number of clinical trials have been conducted studying its effects via epidural, intrathecal, IM, sublingual, and transdermal delivery routes. Epidural buprenorphine has been found to produce postoperative analgesia in patients after coronary artery bypass surgery (CABG).[21] It has been shown that buprenorphine administered by lumbar epidural for analgesia after CABG compares favorably with the same drug delivered via the thoracic route in terms of quality of analgesia and incidence of side effects. Mehta et al.[21] compared the effects of buprenorphine given through both the lumbar and thoracic epidural routes for postoperative analgesia following CABG. Forty patients with normal left ventricular ejection fractions scheduled for CABG were randomly divided into two groups, the

thoracic epidural analgesia group (n = 19) and the lumbar epidural analgesia group (n = 20). For postoperative pain relief, both groups received epidural buprenorphine 0.15 mg at the first demand for pain relief following extubation. A top-up dose of buprenorphine of 0.15 mg was administered in cases where visual analog pain score (VAS) was > 3 one hour after the first dose. Subsequent breakthrough pain was treated with 30 mg IM ketorolac. Pain assessed by VAS score on a 0 to 10 scale, respiratory rate, one-second forced expiratory volume, forced expiratory vital capacity, mean arterial blood pressure, cardiac index, $PaO_2$, and $PaCO_2$ were measured at frequent intervals. The results showed that buprenorphine administered by the lumbar route for analgesia after CABG compared favorably with the same drug delivered via the thoracic route in terms of quality of analgesia.

Buprenorphine has been shown to prolong postoperative analgesia and therefore could have a valuable role in preemptive analgesia. Buprenorphine has been widely used for postoperative analgesia in laboratory animals. Clinical efficacy has been demonstrated in both subjective and objective pain assessment schemes.[22] Previous studies in humans have also reported that epidural buprenorphine has clinical advantages greater than or equal to those of epidural morphine.[23] Miwa et al.[24] studied the effect of epidural buprenorphine on minimum alveolar concentration of volatile anesthetics, duration of analgesia, and respiratory function in the perioperative period. The study involved 120 patients (ASA I-II) undergoing gynecological surgery. The patients were divided into three studies, and the 40 patients in each study were randomly divided into four groups depending on the dosage: Group I (control), Group II ( 80 µg/kg of morphine), Group III (4 µg/kg of buprenorphine), and Group IV (8 µg/kg of buprenorphine). Postoperative analgesic effects were assessed by the total usage of pentazocine as a rescue medication in the 48 hours after surgery. The results showed that epidural buprenorphine administered in a dose of 4 or 8 µg/kg provided postoperative analgesia that was no less effective than that of morphine.

Buprenorphine, being a lipophilic drug, is absorbed at a very slow rate into the cerebrospinal fluid. This quality, coupled with its high affinity for and very slow dissociation from µ receptors, makes the systemic side effects of somnolence, hypotension, urinary retention, and respiratory depression uncommon. In a study by Giebler et al.,[25] only one patient out of 4,000 patients who received epidural buprenorphine suffered from respiratory depression.

The mode and site of analgesic action of epidural buprenorphine was studied in human gastrectomy patients by Inagaki et al.[3] Their study supports the hypothesis that epidural buprenorphine is rapidly absorbed from the epidural space into the systemic circulation and produces systemic (supraspinal) analgesia on par with IV buprenorphine administered at the supraspinal region of the central nervous system. Epidural buprenorphine also produces spinal segmental analgesia, which develops two to six hours after administration. Buprenorphine has been used epidurally in the management of pain associated with multiple rib fractures.[26] In that study, nausea, vomiting, and pruritis were the only complications; hypotension, urinary retention, and respiratory depression were not seen.

While epidurally administered buprenorphine in a dose of 4 or 8 µg/kg provides postoperative analgesia that is as effective as that of morphine in a dose of 80 µg/kg,[24] a dose of 15 µg/h may be optimal for postoperative pain relief after lower abdominal surgery.[27] Buprenorphine is not as water-soluble as morphine. In a study of posthepatectomy patients, it was noted that buprenorphine injected at the thoracic level produced good and long-lasting pain relief, whereas buprenorphine injected at the lumbar level produced inadequate analgesia. Morphine injected at either the thoracic or lumbar level produced excellent and long-lasting pain relief.[28] This is probably the result of the difference in water solubility between the two drugs.

In children, administration of buprenorphine through the caudal epidural space has been found to be a safe and reliable means of providing postoperative pain relief for up to 24 hours.[29] One study involved 40 children aged one to 11 years who received general anesthesia for genitourinary surgery, and it compared the quality and duration of analgesia after caudal blocks in two groups of patients. Group I (n = 20) received caudal bupivacaine 0.25 percent, and Group II (n = 20) received caudal buprenorphine 4 µg/kg; each received 0.5 ml/kg body weight. Postoperative behavior and severity of pain were measured using a 3-point scale. The results indicated that, in the immediate postoperative period, caudal buprenorphine provided excellent postoperative analgesia comparable to that observed with caudal bupivacaine. In addition, buprenorphine proved better in the late postoperative period, with analgesia lasting from 20 hours to more than 24 hours. Buprenorphine was associated with fewer side effects compared to caudal bupivacaine in children who underwent genitourinary surgery.[30] In children who underwent lower-extremity orthopedic surgery under general anesthesia, it was shown that postoperative analgesia lasted longer and resulted in fewer side effects in patients receiving buprenorphine caudally at the end of surgery, at a dose of 4 µg/kg body weight, than in those receiving the same amount of buprenorphine IM at the completion of surgery.[31]

In humans, epidural buprenorphine acts predominantly at the supraspinal region and produces spinal segmental analgesia in a dose-related manner.[3] Epidurally administered buprenorphine does not appear to produce urine retention in humans.[32] A retrospective study was conducted using

177 patients after upper and lower abdominal surgery, comparing the efficacy of epidural administration of fentanyl and of buprenorphine for postoperative pain relief. In the fentanyl (F) group, 73 patients received epidural fentanyl 0.1 mg with saline 8 ml postoperatively, followed by a constant-rate infusion of fentanyl 0.025 mg/h for 18 to 24 hours. In the buprenorphine (B) group, 104 patients received buprenorphine 0.2 mg with saline 9 ml epidurally. After upper abdominal surgery, 33 patients (76.7 percent) in F group and 27 patients (52.9 percent) in B group obtained satisfactory analgesia (p < 0.05) as assessed by their verbal analog scores. Respiratory depression occurred in 19 patients in B group and five patients in F group (p < 0.005). It was seen that epidural fentanyl offered a significant advantage compared with epidural buprenorphine for postoperative pain relief following upper abdominal surgery. However, the difference in the degree of analgesia after lower abdominal surgery was not significantly different.[33] This is probably because of differences in the two drugs' lipid and water solubilities.

Intrathecally administered buprenorphine acts as a potent analgesic and as an opioid receptor agonist.[17] Spinal buprenorphine has been used for postoperative analgesia after cesarean section. A study by Celleno et al.[6] compared two doses of intrathecal buprenorphine in 45 women undergoing elective cesarean section under spinal anesthesia. Patients were randomly divided into three groups. Group A (n = 15) received hyperbaric bupivacaine; Groups B and C received the same, but with the addition of 0.03 mg and 0.045 mg buprenorphine, respectively. Patients receiving buprenorphine had a longer pain-free interval than the controls, and within the buprenorphine groups patients receiving the higher dose experienced longer analgesia than those receiving the lower dose. The intrathecal administration of buprenorphine in combination with bupivacaine has been used to relieve intractable pain in patients with vertebral fractures. In addition, intrathecal buprenorphine has been used for the treatment of phantom pain.[34]

Buprenorphine has been widely used as an IV analgesic. The doses that have been described for this route range from 5 to 15 µg/kg, with the higher doses producing postoperative analgesia averaging 13 hours.[35] A study evaluating the efficacy of IV buprenorphine (administered via a patient-controlled analgesia, or PCA, device) in gynecologic patients showed that this drug could be effective in the treatment of postoperative pain, and the potency ratio of buprenorphine to morphine appeared to be 24:1. It can also be used as a parenteral opioid analgesic. Testing of buprenorphine and morphine as postoperative analgesics using PCA devices showed that both analgesics provide adequate analgesia, with no difference in regard to clinical indicators of intestinal motility, VAS, or hospitalization periods. Buprenorphine thus shows synergistic antinociceptive effects in humans with concurrent administration of morphine.[36]

Late antinociception and lower, untoward effects of concomitant intrathecal morphine and IV buprenorphine in humans have been examined by Beltrutti et al.[37] This study was a randomized, double-blinded, placebo-controlled study of patients undergoing hysterectomy with general anesthesia. The patients were divided into three groups. Group I received intrathecal morphine 4.3 µg/kg plus 0.9 percent normal saline IV, Group II received IV buprenorphine 1.3 µg/kg plus intrathecal saline, and Group III received intrathecal morphine 4.3 µg/kg plus IV buprenorphine 1.3 µg/kg. Data from the study showed that the concomitant administration of intrathecal morphine and IV buprenorphine alleviated pain sensation and minimized sedation more effectively than either drug given alone.

Buprenorphine is an effective analgesic when given subcutaneously and could have a role in palliative care and pain control in patients with poor IV access. For patients in the early postoperative period, 30 µg/h was found to be an adequate dose of subcutaneous buprenorphine.[38] Buprenorphine is too poorly absorbed orally in humans to have significant therapeutic value when given via this route.

The sublingual route of administration may be particularly appropriate for highly lipophilic drugs such as buprenorphine.[39] In patients undergoing extracorporeal kidney lithotripsy, it was shown that premedication with 0.2 mg of sublingual buprenorphine provided efficient analgesia with few side effects.[40] Sublingual routes are used with more traditional agents for the management of postoperative pain in patients undergoing prostatectomy.[41] Sublingual buprenorphine as a sole agent provided acceptable postoperative pain relief in about 80 percent of patients who had undergone cholecystectomy, according to a study done by Witjes et al.[42] In this double-blinded, placebo-controlled study involving 125 patients undergoing cholecystectomy, a comparison was made of the quality of postoperative pain relief during patient-controlled intake of sublingual buprenorphine in combination with rectally administered naproxen (1,000 mg/24 hours), paracetamol (4,000 mg/24 hours ), or a placebo. Results obtained in 97 patients were analyzed. The quality of pain relief as measured on a 4-point scale was comparable in all three groups throughout the study. The authors recommended that more elaborate methods, such as IV PCA, might be necessary to achieve good pain relief in the remainder of the patients who did not achieve acceptable postoperative pain relief when patient-controlled intake of sublingual buprenorphine was used as a sole agent.

Buprenorphine can also be administered IM. With this route, the onset of analgesia occurs at 15 minutes, with the peak effect occurring at one hour. The duration of action is six hours, and $T_{1/2}$ is two to three hours.

| Table 1. Buprenorphine dosages in adults | |
| --- | --- |
| **Route of administration** | **Dose** |
| Sublingual | 0.5 to 2.0 mg (single dose) |
| IM | 0.3 to 0.4 mg (single dose) |
| Subcutaneous | 30 μg/h |
| IV | 5 to 15 μg/kg body weight |
| Epidural | 15 μg/h |
| Caudal (in children) | 4 μg/kg body weight |
| Transdermal | 35, 52.5, or 70 μg/h |
| Intrathecal | 0.2 mg (single dose) |

[AU: These data either do not match those presented in the article or represent doses not discussed in the article; consider providing citations. Also, please specify if these doses are for acute or chronic pain.]

Buprenorphine is newly available for delivery in a transdermal formulation. The effects of iontophoresis and electroporation of transdermal buprenorphine from solutions and hydrogels was studied by Fang et al.[43] Their study demonstrated the feasibility of using hydrogels for delivery of buprenorphine with the application of iontophoresis or electroporation, separately or together. A transdermal delivery system (TDS) has recently been developed in the United Kingdom. The system's matrix patch provides rate-controlled administration of the drug. The active drug is incorporated into a polymer matrix which doubles as the adhesive layer. The patch controls the rate of delivery and produces stable serum concentrations. It is available in three dose formulations—35, 52.5, and 70 μg/h—and the suggested duration of each patch is three days. It has been reported that the TDS can also be used in patients with chronic nonmalignant pain due to musculoskeletal diseases.[44] The buprenorphine TDS could represent an alternative analgesic modality for the management of pain in patients requiring around-the-clock opioid therapy.

Animal studies have shown that buprenorphine is less effective at treating signs of pain associated with organ failure or systemic disease than at ameliorating pain associated with surgical incisions and orthopedic, dental, and ophthalmic procedures.[45] Buprenorphine may also have an anti-inflammatory effect. In a rat model of arthritis, oral buprenorphine appeared to have a significant anti-inflammatory effect and to modulate the destructive arthritic phase in joints.[46] Identification of peripheral opioid receptors in inflamed synovia gave rise to the notion of peripheral opioid analgesia in the disease state. Intra-articular buprenorphine and intra-articular bupivacaine produced equally good postoperative pain control, and both allowed for significant reduction in analgesic requirement after knee arthroscopy.[47] A study done by Candido et al.[48] showed that buprenorphine and local anesthetic delivered by axillary perivascular brachial plexus block provided postoperative analgesia lasting three times longer than local anesthetic block alone, and twice as long as buprenorphine given by IM injection plus local anesthetic block. This supports the concept of peripherally mediated opioid analgesia by buprenorphine.

## APPLICATIONS IN CHRONIC PAIN

An interesting study in rats suggested that buprenorphine may be a useful analgesic for treating neuropathic pain after spinal cord and peripheral nerve injury.[49] This study was based on several unique properties of buprenorphine. In addition to its unique μ, κ, and δ receptor affinities, buprenorphine induces nociception that is not sensitive to pretreatment with pertussis toxin, which uncouples many G proteins.[50] Increased coupling of G proteins in the spinal cord could lead to antinociception in neuropathic pain states. Recent evidence also suggests that the antinociceptive actions of buprenorphine may be mediated by mechanisms that are very different from those of classical μ agonists such as morphine. The 2002 study by Kouya et al.[49] compared the antinociceptive and antihyperalgesic effects of buprenorphine in normal and neuropathic rats. In normal rats, systemic buprenorphine produced dose-dependent antinociception in the hot-plate test. In rats with peripheral nerve and/or spinal cord injury, buprenorphine markedly alleviated neuropathic-pain-related behaviors, including mechanical and cold allodynia/hyperalgesia, at

doses comparable to that producing antinociception. The results suggested that buprenorphine may be a useful analgesic for treating neuropathic pain, unlike other opioids, such as morphine, which tend to be less potent after nerve injury.

Sublingual buprenorphine has recently been seen to be effective in the treatment of chronic pain syndrome. Many patients with chronic pain have suboptimal therapeutic outcomes, with associated worsening of pain perception, functional capacity, and mood after prolonged treatment with opiate analgesics. Malinoff et al.[51] recently studied 95 patients who had undergone failed long-term opiate analgesic treatment. The length of therapy ranged from 1.5 to 27 years. After a minimum of 12 hours of abstinence from all opiate analgesics, patients were given low doses of sublingual buprenorphine or buprenorphine/naloxone. The mean duration of treatment was 8.8 months. Eighty-six percent of the patients experienced moderate to substantial relief of pain, accompanied by improved mood and functioning. Sublingual buprenorphine and buprenorphine/naloxone appeared to be well tolerated, safe, and effective in the treatment of chronic pain refractory to long-term opiate analgesics in this study.

The increasing importance of buprenorphine in the treatment of chronic pain was recently attested to by an interesting study in a human pain model in Germany. Koppert et al.[52] studied the time course of analgesic and antihyperalgesic effects of IV and sublingual buprenorphine in the human pain model. In a randomized, double-blinded, placebo-controlled crossover study, transcutaneous stimulation was used to repetitively assess the magnitude of pain and the area of secondary hyperalgesia before and up to 150 minutes after administration of 1) 0.15 mg buprenorphine IV and placebo pill sublingually, 2) 0.2 mg buprenorphine sublingually and saline 0.9 percent IV, or 3) saline 0.9 percent IV and placebo pill sublingually as a control. For both applications of buprenorphine, the antihyperalgesic effects were more pronounced compared to the analgesic effects (66 ± 9 vs. 26 ± 5 percent, and 43 ± 10 vs 10 ± 6 percent for IV and sublingual applications, respectively). This contrasts with the pattern for the IV administration of pure $\mu$ receptor agonists in the same model, in which the antihyperalgesic effects are weaker. The half-lives of buprenorphine-induced analgesic and antihyperalgesic effects were 171 and 288 minutes, respectively. In contrast with pure $\mu$ receptor agonists, buprenorphine exerted a lasting antihyperalgesic effect in this model. Buprenorphine appears to have potential for improved treatment of difficult chronic pain states with central sensitization.

## ROLE OF BUPRENORPHINE IN OPIOID DEPENDENCE

Opioid addiction is a chronic, relapsing disorder. Without treatment, high morbidity and mortality rates are seen. Pharmacotherapies for this disorder using $\mu$ receptor agonists (methadone and levomethadyl acetate) and partial agonists have been being developed for the last 40 years.[53] Buprenorphine has pharmacodynamic effects very similar to those of typical $\mu$ agonists such as morphine and heroin.[54] Differing results with buprenorphine have been reported concerning its relative effectiveness in the maintenance treatment of opioid-dependent individuals. In an integrated review by Mattick et al.,[55] buprenorphine given in flexible doses appeared statistically significantly less effective than methadone in retaining patient in-treatment. The authors concluded that buprenorphine was an effective intervention for use in the maintenance treatment of heroin dependence, but when used as a solo agent it appeared to offer no advantages over methadone. Buprenorphine-carbamazepine, however, appeared to be more effective than methadone-carbamazepine in detoxification strategies for opioid addicts with additional multiple-drug abuse.[56] The FDA has approved the marketing of buprenorphine in sublingual tablets, both alone (Subutex) and with naloxone (Suboxone), for treatment of opioid dependence.

The final rescheduling of buprenorphine from a Schedule V narcotic to a Schedule III narcotic came out in the *Federal Register* in October 2002. This rule imposed regulatory controls and criminal sanctions pertaining to a Schedule III narcotic on those persons who handle buprenorphine or buprenorphine products. Those substances classified as Schedule III are defined as having less abuse potential than Schedule I and II drugs, including morphine and fentanyl (methadone is a Schedule II drug).[57]

Buprenorphine in high doses became available in France in 1996 as a substitute treatment for heroin addicts. Because of its actions as a partial $\mu$ opioid agonist and $\kappa$ opioid antagonist, buprenorphine is currently used as a maintenance medication for heroin-dependent subjects. The unique pharmacological properties of buprenorphine, along with its high patient-acceptance rate, favorable safety profile, and ease of clinical administration, should facilitate its incorporation into treatment programs.[12] Buprenorphine hydrochloride is sold under the trade name of Buprenex. It produces opiate detoxification with a minimum of commonly associated discomfort. During detoxification, Buprenex allows for comfortable, painless withdrawal, without the fatigue, sweats, tactile-sensation complaints ("tingling" or "skin-crawling"), aches, seizures, or confused thought processes common during traditional detoxification procedures. Transfer from methadone to buprenorphine can safely occur from doses of around 30 mg of methadone.[58] Previous studies have shown 8 mg of sublingual buprenorphine to be equivalent to 60 mg of oral methadone in terms of retention rate and opioid-negative urine levels. Strong demonstrations of symptom-free

detoxification from heroin can be obtained with a single high dose of buprenorphine.[59]

Buprenorphine is used as a partial opioid agonist for treating addicted patients who are pregnant. Aromatase is the major enzyme involved in the metabolization of buprenorphine in the human placenta. Buprenorphine is secreted in breast milk and should not be used in nursing mothers.[60]

### Anesthesia– and buprenorphine–assisted heroin detoxification

In the last 15 years, expensive, ultrarapid, anesthesia-assisted opioid clearance and antagonist-induction procedures have been widely publicized as a convenient way to withdraw from opioids. These procedures are fraught with serious risks, including multiorgan failure and persistent withdrawal symptoms. A recent, important, controlled study by Collins et al.[9] examining buprenorphine-assisted detoxification for the positive control group showed data that do not support the use of general anesthesia for heroin detoxification and rapid opioid-antagonist induction. The researchers employed buprenorphine-assisted rapid detoxification with naltrexone-induction interventions in their study, in addition to anesthesia-assisted rapid opioid detoxification with naltrexone induction and clonidine-assisted opioid detoxification with delayed naltrexone induction. A total of 106 heroin-dependent patients seeking treatment were randomly assigned to one of these three groups and underwent 72 hours of inpatient treatment, followed by 12 weeks of outpatient naltrexone maintenance with relapse-prevention psychotherapy. Compared with clonidine-assisted detoxification intervention, the anesthesia- and buprenorphine-assisted detoxification interventions had significantly greater rates of naltrexone induction (94 percent with anesthesia, 97 percent with buprenorphine, and 21 percent with clonidine), but the groups did not differ in rates of completion of inpatient detoxification. The treatment retention rates over 12 weeks were also not significantly different among the groups, with 20 percent retained in the anesthesia-assisted group, 24 percent in the buprenorphine-assisted group, and 9 percent in the clonidine-assisted group. There was also no significant difference in proportions of opioid-positive urine specimens. The anesthesia procedure was associated with three potentially life-threatening adverse events and could therefore be a potentially dangerous approach to treating opioid dependence.

### BUPRENORPHINE AND CANCER PAIN

Buprenorphine has certain unique properties which make it suitable for the treatment of cancer pain. Its properties of being a broad-spectrum, highly lipophilic, and long-acting partial $\mu$ receptor agonist that is non-cross-tolerant to other opioids makes it particularly attractive

| Table 2. Potential clinical applications of buprenorphine |
|---|
| **Epidural for postoperative pain control following:** |
| Lower-extremity surgery |
| Gynecological surgery |
| CABG |
| Multiple rib fracture |
| Gastrectomy |
| Hepatectomy |
| Genitourinary surgeries |
| Upper and lower abdominal surgeries |
| **Intrathecal uses:** |
| Vertebral fractures |
| Phantom pain |
| Elective cesarean section |
| **IM for postoperative pain following:** |
| Lower-extremity orthopedic surgeries |
| **Sublingual for postoperative pain following:** |
| Cholecystectomy |
| Extracorporeal kidney lithotripsy |
| Opioid-addiction treatment |
| **IV for postoperative pain control following:** |
| Gynecological surgeries |
| Cesarean section |
| Suprapubic prostatectomies |
| **Transdermal administration for:** |
| Moderate to severe cancer pain |
| Noncancer pain |
| Chronic pain |
| Back pain |
| Osteoarthritis |
| Osteoporosis |

for use in cancer patients. Constipation is a common problem in cancer patients. It has been observed that constipation and sexual dysfunction appear to be less severe with buprenorphine than with other opioids. As mentioned above, buprenorphine can be given via several routes. The development of a polymer-matrix delivery system for buprenorphine facilitates pain management in cancer patients who are unable to take oral analgesics. The combination of buprenorphine with naloxone in sublingual preparations for cancer patients unable to take oral opioids also helps prevent illicit conversion of prescriptions for parenteral administration. Buprenorphine may thus have particular advantages over other opioids in the treatment of cancer pain.[61]

## BUPRENORPHINE IN OPIOID–TOLERANT PATIENTS

Increasing numbers of patients are being found to have a history of opioid tolerance when they are admitted for the treatment of acutely painful conditions. One of the major concerns surrounding the use of buprenorphine in patients with opioid tolerance has been the traditional belief that some symptoms of withdrawal could result. This concern arises from the fact that buprenorphine binds tightly to the μ receptor. Clinical experience treating acute pain with buprenorphine in patients receiving maintenance therapy is limited.[62] The available literature suggests that acute pain can be effectively managed with as little as 0.4 mg of buprenorphine given sublingually every eight hours in patients who are opioid naïve.[63] However, these low doses may not provide effective analgesia in patients with opioid tolerance who are receiving opioid agonist therapy. Therefore, in addition to divided dosing of buprenorphine, effective analgesia may require the use of additional opioid agonist analgesics (e.g., morphine). If the patient is hospitalized with acute pain, his or her baseline opioid requirement should be given, and opioid withdrawal should be prevented by converting buprenorphine to methadone at 30-40 mg/day. Methadone, at this dose, will prevent acute withdrawal in most patients, and unlike buprenorphine it binds less tightly to the μ receptor.[64] If opioid withdrawal persists, subsequent daily methadone doses can be increased in 5 to 10 mg increments.[62] Caution should therefore be exercised in using buprenorphine in opioid-tolerant patients, since buprenorphine can precipitate opioid withdrawal.

## SIDE EFFECTS OF BUPRENORPHINE

Respiratory depression can occur with too high a dosage, but life-threatening respiratory depression is much less likely with buprenorphine than with a pure μ agonist such as heroin or methadone. Its common side effects of confusion, hallucination, blurred vision, dry mouth, and lightheadedness are seen with other antagonist analgesics as well.[65]

Buprenorphine can cause typical opioid effects such as sedation, nausea, itching, constipation, and, in higher doses, even addiction; however, good titration results in minimal side effects. Respiratory depression caused by buprenorphine can be reversed by naloxone.[66] Severe myositis and rhabdomyositis leading to sciatic neuropathy were reported in two patients abusing buprenorphine by crushing and dissolving tablets for IV use.[67] Data have suggested that buprenorphine and other drugs from its family are capable of producing considerably higher levels of cognitive failure as compared to other pure μ agonists.[68] Opioid rotation should be tried if this side effect is encountered.

Assessment of cognitive tests measuring psychomotor performance in patients maintained with buprenorphine showed that buprenorphine produced less impairment of cognitive functions in some areas than methadone. This difference was seen in the areas of driving ability and social functioning.[69]

## CONCLUSION

Recent interest in and research on buprenorphine have shown that it is an even more important analgesic than previously thought, useful for controlling acute postoperative pain, nonacute pain, and possibly chronic neuropathic pain. It is being used extensively in Europe at the current time for antinociception, and there is possibly an important role for the drug in the treatment of patients with chronic pain displaying suboptimal therapeutic outcomes after prolonged treatment with opiate analgesics.

Buprenorphine, in clinical doses, appears to have a dose-related isoflurane-sparing effect in the rat, similar to that seen with morphine. In laboratory studies, buprenorphine resulted in less cardiovascular and respiratory depression and had a longer-lasting action than morphine, suggesting a potential anesthetic-sparing effect.[70] Despite this anesthetic-sparing effect, buprenorphine's use with ketamine/medetomidine may be associated with an increased risk of anesthetic-related mortality in rats, in both transdermal and transmucosal formulations.[71] It is clear that buprenorphine's role as an anesthetic-sparing opioid requires further investigation.

The unique physicochemical properties of buprenorphine, including its low molecular weight and high analgesic potency, make it an excellent compound for transdermal delivery. It is widely used in Europe via this route, and clinical trials are under way in the United States with the aim of approving it for use via this route.

Buprenorphine has been shown to be a safe and effective alternative to morphine in patients with acute pain. More work needs to be done to determine its efficacy in opioid rotation and opioid conversion. More research

also needs to be done regarding its mechanism of action for antinociception and to determine its role as an anti-inflammatory agent, its effect on the immune system, and its usefulness in myocardial protection and in the treatment of neuropathic pain. The potential of buprenorphine for use as an antihyperalgesic medication should also be considered.

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*Roberta L. Hines, MD, Professor and Chair of Anesthesiology, Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut.*

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