

Review Article

Buprenorphine: Considerations for Pain Management

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Abstract

New effective analgesics are needed for the treatment of pain. Buprenorphine, a partial mu-opioid agonist which has been in clinical use for over 25 years, has been found to be amenable to new formulation technology based on its physiochemical and pharmacological profile. Buprenorphine is marketed as parenteral, sublingual, and transdermal formulations. Unlike full mu-opioid agonists, at higher doses, buprenorphine's physiological and subjective effects, including euphoria, reach a plateau. This ceiling may limit the abuse potential and may result in a wider safety margin. Buprenorphine has been used for the treatment of acute and chronic pain, as a supplement to anesthesia, and for behavioral and psychiatric disorders including treatment for opioid addiction. Prolonged use of buprenorphine can result in physical dependence. However, withdrawal symptoms appear to be mild to moderate in intensity compared with those of full mu agonists. Overdoses have primarily involved buprenorphine taken in combination with other central nervous system depressants. J Pain Symptom Manage 2005;29:297-326. © 2005 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words

Buprenorphine, pharmacology, pharmacodynamics, pharmacokinetics, pain management, partial agonists, formulations, opioids

Introduction

Buprenorphine has been available worldwide as a parenteral and sublingual analgesic since

the 1970s. Parenteral buprenorphine has been approved for commercial marketing in the United States since December 1981. It is one of

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a number of opioid partial agonists and mixed agonist-antagonists currently approved as analgesics by the Food and Drug Administration (Table 1).¹

Buprenorphine (Figure 1) is a derivative of the morphine alkaloid thebaine^{2,3} and is a member of the 6,14-endo-ethanotetrahydro-orphine class of compounds that includes other potent analgesics such as diprenorphine and etorphine.^{4,5} Although buprenorphine has been shown to interact *in vivo* and *in vitro* with multiple opioid receptors, its primary activity in man is that of a partial agonist at the mu-opioid receptor and antagonist at the kappa receptor.⁶⁻¹⁰ The effects of binding at mu-opioid receptors include supraspinal analgesia, respiratory depression, and miosis. Buprenorphine, being a partial mu-opioid agonist, may have a wider safety profile compared to full mu agonists, especially with regard to respiratory depression. Further, the slow dissociation of buprenorphine from the receptor may result in fewer signs and symptoms of opioid withdrawal upon termination of buprenorphine therapy than those which occur with full mu-opioid agonists, such as morphine, heroin, and methadone. Buprenorphine's antagonist effects at the kappa receptor are associated with limited spinal analgesia, and dysphoria and psychotomimetic effects.¹¹

Several delivery formulations of buprenorphine have been investigated. Oral bioavailability of buprenorphine is low because of extensive first-pass hepatic metabolism.^{12,13} However, buprenorphine has certain physiochemical properties (discussed later) that can allow for other drug delivery technologies to be utilized. The administration of buprenorphine by the sublingual route allows for bypassing of the first-pass hepatic metabolism. Transdermal administration

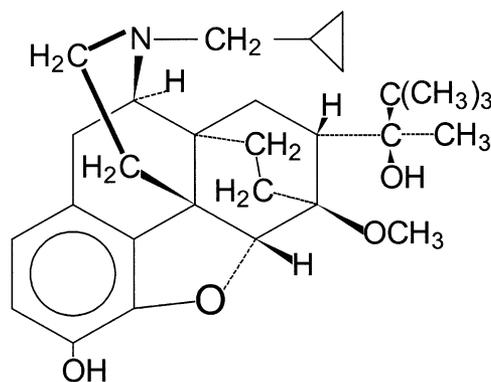


Fig. 1. Chemical structure of buprenorphine. The chemical name of buprenorphine is 6,14-ethenomorphinan-7-methanol, 17-(cyclopropylmethyl)- α -(1,1-dimethylethyl)-4, 5-epoxy-18, 19-dihydro-3-hydroxy-6-methoxy- α -methyl-, [5 α , 7 α , (S)]. The structural formula is described in Reference 2.

has proven clinical utility for numerous medications and provides clinicians the opportunity to treat patients who cannot take oral medications, such as those with head, neck, mouth or bowel lesions, or persistent nausea and vomiting. Both the sublingual and transdermal analgesic dosage forms of buprenorphine are approved for use outside of the United States. In the United States, the sublingual formulation has been recently approved for the treatment of opioid addiction (but not as an analgesic)¹⁴ and a transdermal formulation is under development. Both are discussed in this review.

The purpose of this review is to provide clinicians and researchers with information regarding the appropriate therapeutic use of buprenorphine for pain management, and an understanding of the mechanisms underlying its pharmacodynamic actions. Buprenorphine is approved for use as an analgesic for various

Table 1
Opioid Partial Agonist and Agonist/Antagonists Analgesics Commercially Available for Analgesia in the United States

Medication	Activity at Mu-opioid Receptor	Activity at Kappa-opioid Receptor	Dosage Forms Available	Usual Single Analgesic Dose (mg)	Controlled Substances Act Schedule
Buprenorphine	partial agonist	antagonist	parenteral	0.3	III
Pentazocine	partial agonist or weak antagonist	agonist	parenteral oral	30 50	IV
Butorphanol	partial agonist	strong agonist	parenteral nasal	1-2 1-2	IV
Nalbuphine	antagonist	agonist	parenteral	10	Unscheduled

Adapted from Gutstein and Akil.¹

types of pain (e.g., acute, chronic, and neuropathic pain). It has also been used for treating various behavioral and psychiatric disorders (e.g., depression and opioid dependence).

Preclinical Pharmacology

Receptor Binding/Interactions Studies

In vitro studies have shown that buprenorphine binds with high affinity to mu- and kappa-opioid receptors and relatively lower affinity to delta-opioid receptors.^{15,16} Although most *in vitro* studies have shown buprenorphine to be relatively non-selective for these receptors, others have shown a selective potency of the (-) enantiomer of buprenorphine for $\kappa_1 = \mu > \delta > \kappa_{2a} > \kappa_{2b}$,¹⁷ with a slow dissociation from all receptors.¹⁸

In vivo studies have shown that buprenorphine binds at the mu-opioid receptor,¹⁹ where it is believed that analgesic and other effects (e.g., supraspinal analgesia, respiratory depression, miosis, decreased gastrointestinal motility, and euphoria) are mediated. Buprenorphine is an antagonist at the kappa-opioid receptor; agonist activity at the kappa-opioid receptor is thought to be associated with spinal analgesia, sedation, miosis, and psychotomimetic (i.e., dysphoric) effects. Although buprenorphine binds with high affinity to the delta opioid receptor (but still lower than to the mu or κ_1 receptor), the functional significance of this interaction has not been fully elucidated.¹ More recently, it has been proposed that partial agonist activity at the opioid-receptor-like 1 (ORL-1) receptor, with its endogenous ligand nociceptin or orphanin FQ (N/OFQ), may contribute to the analgesic effect of buprenorphine.²⁰

Buprenorphine Effects in Pain Models

Buprenorphine has been shown to increase the nociceptive threshold to electrical stimulation in the tooth pulp assay in dogs.^{21,22} The antinociceptive potency of buprenorphine in the rat and guinea pig paw pressure tests was noted to be greater than morphine,²³ and buprenorphine was shown to be 10 times more potent than morphine in the formalin test (a model of post-injury pain).²⁴

In addition to the biphasic dose-response curve observed for buprenorphine with regards to effects on respiration in mice and intestinal

motility in rats,²⁵ a bell-shaped dose-response curve for the antinociceptive action of buprenorphine has been observed in certain preclinical pain models (e.g., mouse and rat hot plate, rat and monkey tail dip, and rat electrical stimulation of the tail and formalin-induced flinching),²⁶⁻³¹ whereas a linear dose-response relationship has been observed in others (e.g., rodent writhing and tail pressure).²⁶ A curvilinear dose response for antinociceptive effects was first observed by Cowan and coworkers in the rodent tail dip/flick test,²⁶ and later by Dum and Herz²⁷ in *in vivo* binding studies in the rat. Explanations for this bell-shaped curve include a 2-receptor model and noncompetitive autoinhibition.^{7,17,19,26} The peak of the dose-response curve occurred at a dose of approximately 1 mg/kg. The entire curve shifted to the right following pretreatment with the opioid antagonists naloxone³² or naltrexone.²⁷ Although readily demonstrated in preclinical analgesic studies, the bell-shaped dose-response curve has not been observed in clinical analgesic trials that have utilized much lower doses of buprenorphine. A study (not an analgesic trial) designed to find the peak of this dose-response curve in human subjects used a maximum single dose of 32 mg administered as a sublingual solution.³³ A plateau of subjective and respiratory depressive effects was observed, consistent with the partial agonist classification of buprenorphine (Figure 2); however, the effects were not biphasic even in this dose range.

Distinguishing (Discriminative) Stimulus Properties and Self-Administration

In studies where animals were trained to distinguish between an opioid (e.g., morphine) and no drug (e.g., saline), buprenorphine generalized to medications such as morphine and fentanyl.^{34,35} These results indicated that the internal drug cues produced by buprenorphine are similar to those of the other opioids. Animals that have previously been made dependent on morphine will acquire drug-taking behavior (i.e., self-administration by pressing a lever that activates administration) when exposed to morphine-like drugs. Albeit sometimes weakly, buprenorphine has been shown to support intravenous self-administration in animals under various conditions of reinforcement.³⁶⁻⁴⁰ Both drug-naïve and drug-experienced

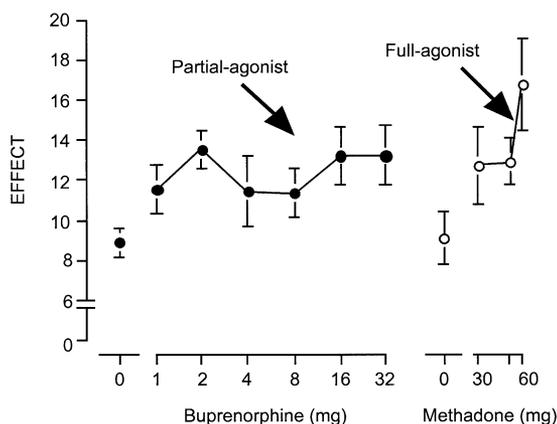


Fig. 2. The effects of the partial-agonist buprenorphine (closed circle) and the full-agonist methadone (open circle) on an opioid agonist scale. The scale contains 16 adjectives descriptive of opioid-like agonist effects rated on a 0–4 ordinal scale (maximum score = 64). Each vertical bar represents ± 1 SEM. Reprinted from Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE, Clinical pharmacology of buprenorphine: ceiling effects at high doses. *Clinical Pharmacology and Therapeutics*, 1994, 55: 569–580,³³ with permission from the American Society for Clinical Pharmacology and Therapeutics.

animals have been shown to self-administer buprenorphine.^{37,38}

Physical Dependence Liability

Three primary preclinical experimental procedures have been used to evaluate the morphine-like physical dependence potential of buprenorphine in animals. The first procedure is the substitution of buprenorphine for morphine in morphine-withdrawn animals. The second is the precipitation of an opioid abstinence syndrome by buprenorphine in morphine-dependent animals. The third is the substitution of placebo (i.e., saline) to assess the presence of spontaneous withdrawal in buprenorphine-maintained animals.

In studies of the above-described procedures, buprenorphine has been shown to produce either no, or a protracted but mild, opioid-like withdrawal syndrome in rats, dogs, and non-human primates.^{6,26,27,37,41,42} For example, Martin and coworkers showed that in dogs maintained on 125 mg/day morphine, at low doses, buprenorphine substituted for morphine (i.e., suppressed spontaneous withdrawal) and at higher doses, precipitated an abstinence syndrome.⁶ Buprenorphine was also reported to

precipitate an abstinence syndrome in rhesus monkeys maintained on morphine.⁴³ In another study, no signs of opioid withdrawal were observed when saline was substituted for chronically-administered buprenorphine in rhesus monkeys, and there were no signs of disruptions in other behaviors such as food intake.³⁷ Taken together, the ability of buprenorphine to generalize to morphine-like drugs along with its production of only relatively mild physical dependence indicates that buprenorphine's potential for abuse is limited compared to many other opioids.

Tolerance to the behavioral effects of buprenorphine has been reported in the rhesus monkey.^{38,44} Cross-tolerance of buprenorphine to morphine has been shown in the mouse²⁵ and rat.⁴¹

Safety

The LD₅₀ values for buprenorphine, assessed in a number of animal species by various routes of administration, are shown in Table 2.⁴⁵ Table 3 shows the comparison of the ratio of the acute toxic doses to the antinociceptive doses yielding the therapeutic index for morphine and buprenorphine in rats. These data are consistent with a wide safety margin for buprenorphine.

Studies in mice and rats have shown that buprenorphine is not a carcinogen at doses 1600 times greater than the analgesic dose. From genetic toxicity studies, including the Ames test, the chromosomal aberration assay, and the mouse lymphoma forward mutation assay, it has been concluded that buprenorphine is not a mutagen and presents no genetic danger to man.

Table 2
Acute Toxicity (LD₅₀) of Buprenorphine

Species	Route of Administration	LD ₅₀ (mg/kg)	
		Base	HCl salt
Mouse	oral	260	800
Mouse	intravenous	24	72
Mouse	intramuscular	–	>600
Mouse	intraperitoneal	90	–
Mouse	subcutaneous	–	>1000
Rat	oral	–	>1000
Rat	intravenous	31	62
Rat	intramuscular	–	>600
Rat	intraperitoneal	197	–
Rat	subcutaneous	–	>1000
Dog	intravenous	–	79

–Data not available. Reference 45.

Table 3
Therapeutic Indices for Morphine
and Buprenorphine

Opioid	LD ₅₀ , Acute (mg/kg)	ED ₅₀ , Tail Pressure (mg/kg)	Therapeutic Index LD ₅₀ /ED ₅₀
Morphine	306 [237, 395]	0.66 [0.26, 1.6]	464
Buprenorphine	197 [145, 277]	0.016 [0.011, 0.024]	12,313

References^{25,26}
Numbers in brackets are 95% confidence limits.

Although buprenorphine has been reported to be without teratogenic effects in rodents,⁴⁶ significant increases in skeletal abnormalities were noted in rats after subcutaneous administration of 1 mg/kg/day and greater, but not at oral doses up to 160 mg/kg/day.¹⁴ Increases in skeletal abnormalities in rabbits after intramuscular administration of 5 mg/kg/day, or 1 mg/kg/day or more given orally were not statistically significant. Buprenorphine produced statistically significant pre-implantation (oral doses of 1 mg/kg/day or more) and post-implantation (intravenous doses of 0.2 mg/kg/day) losses in rabbits.¹⁴

Unlike effects observed from some other opioids, prenatal exposure in rats to buprenorphine does not appear to affect activity, cycles of rest-activity, or developmental milestones.⁴⁶⁻⁵² The oral administration of buprenorphine to rats during gestation and lactation, at doses several hundred times greater than the analgesic dose, has been associated with delayed postnatal development of the righting reflex and startle response.^{14,53} It has been reported that buprenorphine reduces striatal nerve growth factor⁵⁴ and produces toxic effects similar to methadone.⁵² Mixed effects of buprenorphine on maternal water intake, postnatal growth, maternal weight gain, frequency of resorption, or pup birth weights, number of stillbirths, and offspring mortality have also been reported.^{14,52,55-57} Physical dependence and tolerance to the antinociceptive effects of morphine in pups exposed perinatally to buprenorphine and methadone have been demonstrated; generalized neuromuscular development does not appear to be delayed by perinatal exposure to buprenorphine.⁵⁷

Pharmacokinetics

General Observations

Buprenorphine is an extremely lipophilic compound⁵⁸ that dissociates very slowly from

the mu-opioid receptor.^{18,58-60} This slow receptor dissociation has generally been regarded as the property responsible for buprenorphine's relatively long duration of action as an analgesic. Buprenorphine also has a high affinity for the mu-opioid receptor, and is not displaced easily by antagonists, such as naloxone, which have a lower receptor affinity.⁶¹

The elimination half-life of buprenorphine in humans has been described as either biphasic⁶² or triphasic.^{63,64} Buprenorphine is highly bound (96%) to plasma proteins, primarily to α - and β -globulin fractions.⁶⁵ Studies utilizing human liver microsomal preparations indicated that buprenorphine is demethylated to form norbuprenorphine, and is also metabolized to other compounds by cytochrome P-450 3A4.^{66,67} Both buprenorphine and norbuprenorphine form conjugates with glucuronic acid.^{68,69} Studies in rats utilizing intraventricular administration of norbuprenorphine and buprenorphine indicated that the intrinsic analgesic activity of norbuprenorphine was 25% that of buprenorphine.⁷⁰

The oral bioavailability of buprenorphine is approximately 10%, secondary to extensive first-pass hepatic metabolism.^{12,71} Preclinical studies in rats indicate that buprenorphine distributes rapidly to the brain following intravenous administration.⁷⁰ Brain to plasma concentration ratios of buprenorphine in rats following a single intravenous dose ranged from 3.0 at 15 minutes to 10.5 at 6 hours post-drug administration.⁷² The more polar metabolite norbuprenorphine has an n-octanol:water partition coefficient about 10% that of buprenorphine⁷⁰ and penetrates into the central nervous system to a much lesser degree than the parent compound.⁷³ In the rat, dog, monkey, and human, approximately 70% or more of an intravenous dose is recovered in the feces;⁷⁴ enterohepatic recycling is likely.⁷⁵ A much lesser percentage of buprenorphine (10-30%) is found in the urine following administration by various other routes.^{65,75} Concentrations found in human red blood cells are comparable to those in the plasma.⁶³

Parenterally Administered Buprenorphine

In the United States, buprenorphine, used as an analgesic, is only approved for parenteral administration, typically by the intramuscular

or intravenous route. Peak plasma concentrations following intramuscular administration occurred, in general, 5 minutes after dosing, and in some patients, by 2 minutes.⁶³ Mean plasma concentrations of buprenorphine in that study differed little after 5 minutes post-drug administration by either the intravenous or intramuscular routes; intramuscular bioavailability ranged from 40% to greater than 90%. The volume of distribution at steady state has usually been found to be between 200 and 400 liters.⁷⁶

Following the administration of 0.3 mg of intravenous buprenorphine given intraoperatively, the initial half-life was found to be about 2 minutes,⁶³ with a mean terminal half-life of 5 hours.⁷⁷ A study by Mendelson and coworkers⁷⁸ indicated that the mean terminal half-life of intravenously given buprenorphine (1 mg infused over 30 minutes) was about 6 hours. Kuhlman and colleagues⁷⁹ reported a mean terminal half-life of 3.2 hours following single doses of 1.2 mg given intravenously.

Buprenorphine clearance following intravenous administration has typically been reported to be between 70 and 80 liters/hour when doses in the analgesic range have been used.^{63,79} The clearance of buprenorphine in anesthetized patients was found to be lower than in the same individuals not under anesthesia secondary to reduced hepatic blood flow from the anesthetic.⁶³

Buprenorphine Sublingual Liquid/Buccal Strip

The absorption of buprenorphine liquid from the sublingual mucosa is rapid, occurring within 5 minutes.⁸⁰ In a study utilizing healthy volunteers,^{80,81} the bioavailability of buprenorphine in a 30% ethanol solution administered sublingually was approximately 30%. Kuhlman and colleagues⁷⁹ studied the pharmacokinetics of buprenorphine by various routes of administration using a crossover design in healthy, non-dependent men who had a history of heroin abuse. Buprenorphine bioavailability by the sublingual and buccal routes was approximately 51% and 28%, respectively, with much interindividual variability. The mean terminal half-lives were 28 hours following sublingual administration and 19 hours following buccal administration, compared with 3.2 hours following the intravenous route, perhaps related to the sequestering of buprenorphine in

the oral mucosa. Average clearances for the 3 routes of administration were 210, 712, and 77 liters/hour, respectively. In a study that evaluated sublingual dosages of buprenorphine up to 32 mg,³³ peak plasma concentrations of buprenorphine were observed at 60 minutes following doses of 2 and 4 mg, and at 30 minutes for doses of 8, 16, and 32 mg. Plasma concentrations after administration of the 32 mg dose were significantly elevated for up to 60 hours following medication administration. As noted previously, the oral bioavailability of buprenorphine is very low (approximately 10%). Thus, the swallowing of buprenorphine that is not absorbed buccally or sublingually would contribute little to overall absorption.

Buprenorphine Sublingual Tablets

Following the sublingual administration of 0.4 or 0.8 mg doses, there was no significant rise in buprenorphine plasma concentrations for 20 minutes; the time to maximum concentration was variable, ranging from 90 to 360 minutes.^{76,77} The average systemic bioavailability was 55%, with large intersubject variability.

A number of studies have assessed the pharmacokinetic profile of a buprenorphine tablet formulation. Bioavailability of the tablet was reported to be approximately 50–65% that of the sublingual solution, based on 48- and 24-hour AUC measurements, respectively.^{82,83} Results were generally comparable regardless of whether buprenorphine was administered as a single dose, or administered once daily over multiple days. When buprenorphine tablets were given over multiple days, average concentrations peaked 2 hours after medication administration, in contrast to 1 hour as has been found for the solution.

Buprenorphine for Intranasal Administration

The bioavailability of intranasal buprenorphine has been assessed in humans⁸⁴ and sheep⁸⁵ using a polyethylene glycol 300 (PEG) and a 5% dextrose vehicle. The buprenorphine formulation in humans was found to be approximately 50% bioavailable, with a time to maximum concentration of 30 minutes. In sheep, the bioavailability of buprenorphine in PEG and dextrose was 70% and 89%, respectively; time to maximum concentration was 10 minutes. From these data, it appears that an intranasal formulation of buprenorphine would

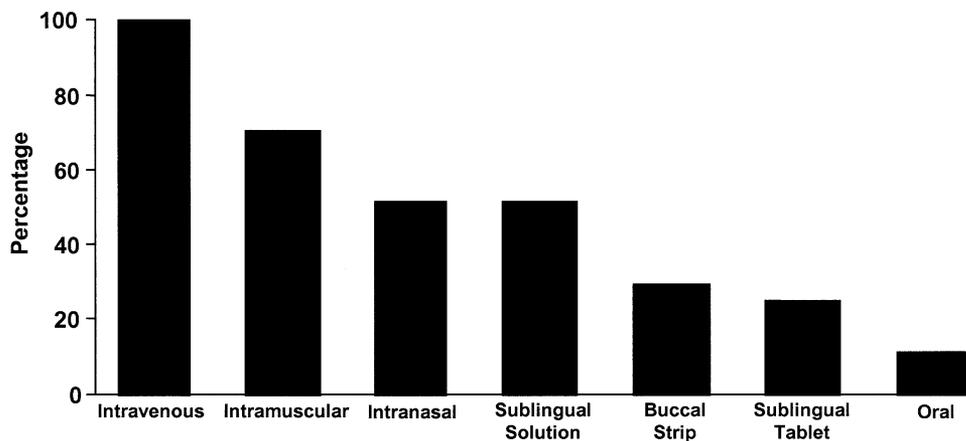


Fig. 3. Approximate bioavailability of buprenorphine by route of administration. Reprinted from Methadone Treatment for Opioid Dependence [Figure 13.2 (c)]. Strain, Eric C., M.D., and Maxine L. Stitzer, Ph.D., eds. The Johns Hopkins University Press. Baltimore, Maryland: The Johns Hopkins University Press, 1999: 300. Reprinted with permission from The Johns Hopkins University Press.

provide a rapid onset of analgesic effect. The approximate bioavailability of buprenorphine by various routes of administration is shown in Figure 3.

Buprenorphine for Transdermal Administration

The ideal medication for transdermal administration should be highly lipophilic and of low molecular weight (less than approximately 1000) for ease of crossing the skin barrier.⁸⁶ It should also be highly potent so that adequate doses could be delivered through the skin. Buprenorphine meets these requirements. It has an octanol-to-water partition coefficient of 1217 (i.e., high lipophilicity),⁸⁷ a molecular weight of 468, and is 25 to 50 times more potent as an analgesic, per mg, than morphine. Further, with a transdermal formulation, a therapeutic blood level could be maintained over an extended period of time, thus improving compliance and effectiveness of the medication.

Recently, a transdermal buprenorphine product has been approved and marketed in a number of European countries.^{88,89} This transdermal system is designed to continuously release buprenorphine at one of three defined rates: 35, 52.5, or 70 $\mu\text{g/hr}$, corresponding to daily doses of 0.84, 1.26, and 1.68 mg/24 hr, respectively. Effective plasma levels are reached within 12 to 24 hours and are kept at a constant level for 72 hours. The buprenorphine is incorporated into a polymer adhesive matrix.

Three dosage strengths of a seven-day buprenorphine transdermal system are being developed in the United States, which deliver 5,

10, or 20 $\mu\text{g/hr}$ buprenorphine, respectively.⁹⁰ The highest strength patch (20 $\mu\text{g/hr}$) will result in a dosage of 0.48 mg/day. Compared to the higher-strength European product described above, these three dosage strengths may be more useful for milder pain syndromes. The buprenorphine is dissolved in a polymer matrix and the rate of drug release is controlled by the diffusion of the buprenorphine in the adhesive matrix through the stratum corneum of the epidermis. The concentration of buprenorphine mixed in the adhesive matrix is the same for each strength. After application of the transdermal system with release rates of 5, 10, and 20 $\mu\text{g/hr}$ to healthy subjects, mean ($\pm\text{SEM}$) peak buprenorphine plasma concentrations (C_{max}) were 176 ± 34 , 191 ± 19 , and 471 ± 77 pg/mL, respectively.⁹⁰ The concentration of buprenorphine released from each system per hour is proportional to the surface area of the system. The time to reach steady-state plasma concentrations was approximately 24 to 48 hours and the percentage of the total dose delivered in 7 days was 15%.⁹⁰ Following system removal, concentrations decreased to about one-half in 12 hours, then declined more gradually with an apparent terminal half-life of 26 hours.^{90,91}

Special Considerations

Buprenorphine in Renal Failure. The disposition of buprenorphine in patients with renal failure

was examined in studies utilizing both single- and multiple-dosing.⁹² In the single-dose study using balanced anesthesia, buprenorphine was given intravenously at a dose of 0.3 mg. In the multiple-dose study, a variable-rate infusion was utilized with controlled ventilation to provide analgesia in the intensive care unit (median infusion rate of 161 $\mu\text{g/hr}$ for a median of 30 hours). In the first study, there were no differences in buprenorphine kinetics between healthy patients and those with renal failure (all dialysis-dependent with creatinine clearances less than 5 mL/min). Buprenorphine clearances and dose-corrected plasma concentrations were similar in the 2 groups of patients. However, in patients with renal failure (plasma creatinine concentration greater than 140 $\mu\text{mol/liter}$), plasma concentrations of norbuprenorphine were increased by a median of 4 times, and buprenorphine-3-glucuronide by a median of 15 times.

Another study, which measured only buprenorphine (not metabolites) over a 3-hour sampling period, reported that the disposition of buprenorphine was similar in patients with end-stage renal failure compared to healthy controls.⁹³ The renal failure patients did not show clinical evidence of sedation or respiratory depression.

Buprenorphine in Hepatic Failure. Few data are available with regard to the use of buprenorphine in patients with hepatic failure. A recent study evaluated the pharmacokinetic profile of buprenorphine (0.3 mg given intravenously) in subjects with mild to moderate chronic hepatic impairment and in healthy controls matched for age, weight, and sex.⁹⁴ No differences between the groups were observed for most pharmacokinetic parameters (e.g., steady-state volume of distribution, total clearance). However, the maximum plasma concentrations of buprenorphine and norbuprenorphine were 50% and 30% lower, respectively, in individuals with hepatic impairment. These subjects also had less nausea and vomiting than the controls. The results did not indicate the need for a buprenorphine dosage adjustment in individuals with mild to moderate chronic hepatic impairment.

Buprenorphine in Children and Infants. When buprenorphine (3 $\mu\text{g/kg}$) was given intravenously as premedication to children aged 4 to

7 years, mean clearance was 3.6 liters/hr/kg and steady state volume of distribution varied from 1.2 to 8.3 liters/kg.⁹⁵ None of the kinetic parameters correlated with age, body weight, or body surface area. Because buprenorphine plasma concentrations declined rapidly, terminal elimination half-life could not be estimated reliably. In a study of the pharmacokinetics of a buprenorphine infusion in premature neonates,⁹⁶ the clearance of buprenorphine was lower than values previously reported for adults and children, probably related to immaturity of the glucuronidation metabolic pathway.

Clinical Pharmacology

Analgesia and Anesthesia

Pain Assessment and Treatment. Pain may be described as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. It is typically categorized broadly as being either acute or chronic. Whereas acute pain is often associated with a particular injury or procedure, chronic pain is pain that has been present for more than three months, and which may be persistent or intermittent. In addition, chronic pain may persist after the disease itself has been effectively treated.⁹⁷

As noted by Bonica,⁹⁸ few basic and clinical scientists had devoted their efforts to pain research prior to the 1960s. Differences between acute and chronic pain were not appreciated, and animal models, particularly for chronic pain, were not being developed. More recently, preclinical and clinical research studies have elucidated multiple mechanisms and sites associated with the production of pain.⁹⁹ Pain itself is subject to much inter-individual variability with regard to threshold and tolerance, and has expectational and emotional components.¹⁰⁰ Thus, all clinical practice guidelines emphasize the need to use patient self-report as the gold standard for assessing pain rather than observers' reports because pain is such a personal experience.

Numerous opioids and opioid-like medications have been used to treat both acute and chronic pain. Chronic pain may involve pain related to cancer, as well as noncancer pain due

to osteoarthritis, chronic back pain, and neuralgia. Although morphine is the prototypical agent, numerous other drugs such as hydrocodone, oxycodone, methadone, and others have been utilized effectively. The use of opioid analgesics for the treatment of chronic noncancer pain, however, still elicits controversy, much of it related to concerns regarding adverse effects and possible addiction.¹⁰¹ It is especially important to differentiate between addiction to opioids and the appropriate use of opioids for analgesia and between addiction and physical dependence. Although patients using opioids for chronic pain may become physically dependent, they usually do not exhibit evidence of behaviors indicative of addiction.¹⁰² Although the treatment of pain in patients with a current or past diagnosis of addiction presents its own unique challenges,¹⁰³ opioids have generally been shown to be safe and effective for the treatment of chronic pain.^{104,105}

Buprenorphine has undergone clinical evaluation for the treatment of acute and chronic pain, analgesic anesthesia, and to a much lesser extent, neuropathic pain. Buprenorphine is indicated for the treatment of moderate to severe pain. Doses of 0.3 mg of buprenorphine are typically considered to produce analgesia approximately equivalent to 10 mg of morphine when both medications are given parenterally.¹⁰⁶⁻¹⁰⁸ As a parenteral analgesic, buprenorphine has been administered by the epidural, intra-articular, intramuscular, intravenous, and subarachnoid routes. It has also been given through the use of subcutaneous implanted micropumps and by continuous subcutaneous infusion.^{3,11,109} The sublingual and transdermal routes of administration have also been utilized. **There are no published data indicating an analgesic ceiling dose in humans.**

Acute Pain. Most studies of acute pain have used 1 or 2 doses of the medication, typically in postoperative patients. One of the earliest assessments of buprenorphine when given parenterally for postoperative pain found that it generally provided good or adequate pain relief with an incidence of less than 1% of drug-associated respiratory depression.¹¹⁰ Various other studies have shown buprenorphine to be as or more effective than morphine as a postoperative analgesic,¹¹¹⁻¹¹⁶ and more effective than meperidine, often with a longer duration of

activity.^{112,117-119} Patients undergoing various types of surgical procedures, including abdominal, gynecological, and cardiac, were evaluated. Nausea/vomiting and dizziness were sometimes more common following buprenorphine administration, but other effects (e.g., decreased respiratory rate, drowsiness) were often observed no more frequently than with the comparison opioid. Further, doubling the intravenous dose of buprenorphine from 0.3 to 0.6 mg has been reported to produce a dose-dependent increase in analgesia without a parallel increase in respiratory depression.⁶⁴ **Doses as high as 7 mg given intravenously for postoperative analgesia have been reported to be without associated respiratory depression.¹²⁰ Although, as noted previously, the dosage at which the peak of the analgesic dose-response curve occurs has been estimated in animal models, there are insufficient data to determine that dosage in humans. Thus, whereas at typical analgesic dosages buprenorphine is approximately 25 to 50 times more potent than morphine, determining potency equivalency at very high doses (such as the 7 mg dose mentioned above) is problematic.**

Wallenstein and coworkers found relative potencies of intramuscular to sublingual buprenorphine of about 2:1 in postoperative cancer patients.¹²¹ The sublingual buprenorphine (tablet formulation) was approximately 15 times more potent than intramuscular morphine. Additionally, the sublingual, but not the intramuscular, formulation was found to be longer acting than morphine.

For the treatment of postoperative pain by the intramuscular route, buprenorphine is about 30 times more potent than morphine.¹⁰⁶⁻¹⁰⁸ In contrast, buprenorphine administered epidurally has been shown to be only about 8 to 12 times more potent than morphine.^{122,123} However, doses of buprenorphine were typically less by the epidural (e.g., 0.06 to 0.15 μg) than by the intramuscular (0.3 mg) route.^{123,124} Although higher epidural buprenorphine doses (0.3 to 0.9 mg) have also been used successfully with a low occurrence of side effects, little additional benefit (as far as duration of action or quality of analgesia) from doses greater than 0.3 mg has been observed.¹²⁵ Pain relief for 12 to 24 hours has typically been observed when buprenorphine is administered epidurally.¹²⁶ Intrathecal buprenorphine, 0.03 or 0.045 mg, with bupivacaine has also been

shown to produce effective, long-lasting analgesia, with nausea and vomiting as the predominant side effects.¹²⁷

With regard to comparisons to other analgesics, buprenorphine has been found to compare favorably to the agonist-antagonist nalbuphine when the medications were given intravenously for pain after abdominal surgery.¹²⁸ Buprenorphine (0.15 mg/mL) or nalbuphine (10 mg/mL) were administered as a continuous infusion at the rate of 0.2 mL/kg per 24 hours. Patients who received buprenorphine had significantly greater pain relief and requested less additional analgesic than those who were given nalbuphine. Compared to pentazocine (30 and 60 mg) in men undergoing orthopedic procedures, buprenorphine (0.3 and 0.6 mg) was associated with less nausea, vomiting, and euphoria, but more sedation, when both medications were given intramuscularly.¹²⁹ Buprenorphine, although more potent, was found to provide equivalent analgesia and a similar side effect profile as pentazocine when both were given intravenously on demand post cholecystectomy.¹³⁰

Sublingually administered buprenorphine has also been shown to be an effective postoperative analgesic.^{76,131-134} Benefits associated with buprenorphine treatment included decreased need for additional analgesics and a long duration of activity. One trial showed that buprenorphine given sublingually (0.4 mg) was associated with less depression of consciousness than when administered intramuscularly (0.3 mg) following major abdominal surgery.¹³⁵ Although lack of salivation was problematic with regard to sublingual administration, instillation of normal saline sublingually was used to overcome this limitation.

A recent study evaluated the efficacy of intra-articular buprenorphine and bupivacaine after knee arthroscopy.¹³⁶ Both buprenorphine (0.1 mg) and bupivacaine (50 mg) were associated with good postoperative pain control and reduced need for analgesia after surgery. Although systemic effects of buprenorphine contributing to its effectiveness could not be ruled out, the low dose of buprenorphine used compared to the therapeutic response observed would seem to argue against this.

Girotra and coworkers found that caudal buprenorphine (4 µg /kg) provided prolonged

analgesia with less nausea and vomiting in children undergoing orthopedic surgery compared to buprenorphine administered intramuscularly at the same dose.¹³⁷ Results from other studies have also supported the efficacy of caudal buprenorphine in children.^{138,139}

Patient-controlled analgesia (PCA) utilizing opioids, including buprenorphine, is widely used for the management of postoperative pain. One study of buprenorphine given as sublingual tablets (up to two 0.2 mg tablets every 3 hrs; maximum of 8 tablets in 24 hrs) following cholecystectomy observed that an acceptable level of pain relief was attained in about 80% of the patients.¹⁴⁰ Another study showed that sublingual buprenorphine compared favorably to intramuscular meperidine with respect to pain relief following gynecological surgery.¹⁴¹ Other studies have also shown the utility of PCA with buprenorphine using various routes of administration, including intravenous and intramuscular.¹⁴²⁻¹⁴⁵ The amounts of buprenorphine administered varied based on a number of factors, including the route of buprenorphine administration, type of surgical procedure, and other medications used.

Buprenorphine/naloxone combinations have been evaluated as an analgesic combination to reduce potential abuse, including use in patient-controlled analgesia paradigms.¹⁴⁶ In one study, patients undergoing abdominal or orthopedic surgery were evaluated.¹⁴⁷ They were randomly assigned to receive either buprenorphine or a mixture of buprenorphine and naloxone, with the amount of naloxone equal to 60% that of buprenorphine on a mg basis. Although the admixture decreased both the analgesic and respiratory depressant effects of buprenorphine, it nonetheless provided an adequate analgesic response. In another investigation, single intramuscular injections of either buprenorphine (0.3 mg) or buprenorphine (0.3 mg) with naloxone (0.2 mg) were compared in individuals following abdominal surgery.¹⁴⁸ Patients in both groups had a good analgesic response that lasted for approximately 12 hours, with no significant differences between the groups observed for efficacy. A trial comparing buprenorphine and buprenorphine/naloxone at the same dosages in patients following orthopedic or gynecological surgery produced similar results.¹⁴⁹

Chronic Cancer and Noncancer Pain. Buprenorphine has also been studied for the treatment of chronic cancer pain. One of the earliest studies evaluated sublingual buprenorphine in the dosage range of 0.15 to 0.8 mg per dose for an average duration of 12 weeks of treatment.¹⁵⁰ Ninety-four of 141 cancer patients on the initially offered dosage range of 0.15 to 0.4 mg discontinued participation in the study within 1 week of initiation. Of those who discontinued, approximately one-half (50 patients) discontinued secondary to side effects that included, in order of frequency, dizziness, nausea, vomiting, drowsiness, and lightheadedness. However, no constipation was reported. Another study¹⁵¹ utilizing a range of daily buprenorphine doses between 0.4 and 3.2 mg (median of 1.6 mg for individuals with pain of malignant origin compared to 1.0 mg for those with non-malignant pain) found similar results, with most patients withdrawing secondary to adverse effects or inadequate analgesic response. As in the first study, the early dropout rate was severe, with 26 of the 70 patients discontinuing treatment within one week. No correlation between buprenorphine plasma levels and analgesic response was found.

When single doses of intramuscularly administered buprenorphine (0.3 mg) and morphine (10 mg) were compared, buprenorphine was found to have a longer duration of action.¹⁵² When compared to pentazocine (50 mg given orally), sublingual buprenorphine (0.2 mg) was found to be superior with respect to analgesia, quality of life, and study terminations secondary to side effects when 1 to 2 tablets were administered every 6 to 8 hours.¹⁵³

In a long-term evaluation (representing 9,716 days of treatment) of 139 patients with cancer whose pain was not previously controlled using conventional analgesic approaches, epidural morphine or buprenorphine provided pain relief in 87% of patients.¹⁵⁴ Mean, daily doses of morphine and buprenorphine were 15.6 (range: 2 to 290) and 0.86 mg (range: 0.15 to 7.2), respectively. The mean duration of treatment was 72 days (range: 2 to 700).

Results from a study of 12 opioid-naïve individuals with cancers of various types, and who did not previously respond to nonsteroidal anti-inflammatory agents, indicated similar analgesic efficacy for buprenorphine (0.3 mg) and morphine (3 mg) when both were admin-

istered by the epidural route.¹⁵⁵ Changes in respiratory function indices associated with buprenorphine in this study were judged to be clinically irrelevant.

A continuous subcutaneous infusion of buprenorphine at a rate of 4 µg/kg per day, following the intramuscular administration of 0.004 µg/kg, provided adequate pain relief with few side effects in 10 patients with pain secondary to cancer.¹⁵⁶ Buprenorphine, administered through the use of an external subarachnoid catheter connected to a micropump, has also been used to treat pain associated with various types of cancers.¹⁵⁷ Subarachnoid buprenorphine, 0.06 to 0.15 mg per day titrated to individual response, provided effective analgesia in all 23 patients studied. No respiratory depression was observed, even in one individual who received 0.52 mg in 24 hours secondary to a dosing error.

Fewer studies have been conducted evaluating the use of buprenorphine for chronic noncancer pain than those assessing its utility for cancer pain, and some include a heterogeneous patient population including individuals suffering from both cancer and noncancer pain. In an evaluation of the use of sublingual buprenorphine in individuals over 65 years of age with chronic pain of various etiologies (including osteoarthritis and malignancy), buprenorphine was well tolerated over the 14-day treatment period.¹⁵⁸ Individuals were given 0.1 mg buprenorphine 3 to 4 times daily as required. Patients in the over-80 years age group had a better analgesic response than those aged 65 to 80 years; the incidence of side effects was low.

The analgesic effectiveness of buprenorphine in the treatment of chronic cancer and noncancer pain was assessed in a number of studies using transdermal administration. With regards to the evaluation of the transdermal product already available in Europe (described previously), three randomized, controlled, double-blind trials have been performed. In one, 157 patients with chronic severe pain related to cancer or other disorders and inadequately controlled with so-called "weak" opioids were randomized to receive buprenorphine or placebo patch for up to 15 days. Patients were switched directly from their previous analgesics on day one of the study and rescue medication (sublingual buprenorphine) was available to all participants.¹⁵⁹ Buprenorphine dosages of 35

and 52.5 µg/hr were associated with significantly higher response rates than placebo. Interestingly, the response to the highest buprenorphine dosage tested, 70 µg/hr, did not reach statistical significance, perhaps secondary (as the authors suggested) to fewer patients assigned to this group and the presence of several refractory patients. Only summary data are available for the two other double-blind studies.^{160,161} In the first, patients who had been inadequately treated with weak opioids or 30 mg morphine were randomized directly to one of the three doses of transdermal buprenorphine or placebo. The double-blind phase lasted for 15 days, and no problems were encountered by patients switching from one of the other opioids to buprenorphine. In the second, patients were treated in an open, run-in phase with buprenorphine sublingual tablets. Individuals who obtained at least satisfactory pain relief were then randomized to either 35 µg/hr buprenorphine transdermal or placebo for 9 days. When the daily dose (0.84 mg) delivered by the patch was added to the additional sublingual buprenorphine required, the total dose in the double-blind phase was comparable to the sublingual dose during the run-in phase. The efficacy of this product was also demonstrated in an open-label follow-up study conducted following the completion of the double-blind studies¹⁶⁰ and from a survey of 3,255 patients with chronic pain.¹⁶²

Clinical studies have been conducted with the 7-day buprenorphine transdermal delivery system that is being developed in the United States. Patients with chronic back pain were treated up to 84 days with the buprenorphine transdermal system (5 to 20 µg/hr).¹⁶³ Pain intensity was significantly reduced after treatment with the buprenorphine transdermal system compared to placebo. Another study in patients with pain from osteoarthritis showed higher odds ratio of successful treatment with the buprenorphine transdermal system for up to 28 days compared with placebo.¹⁶⁴ Studies showed similar pain control after treatment with the buprenorphine transdermal system compared with active controls, such as hydrocodone/acetaminophen or oxycodone/acetaminophen.^{163,165} Additionally, the buprenorphine transdermal system was shown to be well-tolerated over long-term study periods, up to 18 months.¹⁶³⁻¹⁶⁶

Even in consideration of the above data, the use of buprenorphine for the treatment of advanced cancer pain cannot be generally recommended because treatment typically requires high doses of opioids and a rightward shifting of the analgesic dose-response curve may occur. Most of the above-cited studies represent small or uncontrolled trials. Further, data supporting the use of buprenorphine for the treatment of cancer-related pain is very limited compared to the data available for many other opioids (e.g., morphine, fentanyl, and oxycodone). Thus, additional large-scale, controlled trials of buprenorphine will be required before the true utility of buprenorphine in this area can be determined.

Neuropathic Pain. The treatment of neuropathic pain with opioid analgesics is controversial. Neuropathic pain is generally thought to be relatively less responsive to opioids; however, analgesia may be obtained when adequate medication doses are administered.^{167,168} It was reported that 85% of approximately 850 patients with noncancer pain benefited from treatment (of up to 14 years' duration) with opioids. Additionally, 67–80% of individuals treated with patient-controlled opioid analgesia for neuropathic pain were responsive to treatment.¹⁶⁹ Buprenorphine injected near the upper cervical or stellate ganglion has been used effectively for sympathetically-maintained pain.^{170,171} Although the buprenorphine literature is limited in this regard, there is evidence that buprenorphine may be effective for treating some types of neuropathic pain.

Preclinical efficacy was assessed in a rodent model that utilized intrathecal administration of pertussis toxin to produce effects similar to symptoms reported by patients suffering from neuropathic pain. Buprenorphine-induced antinociception, unlike the effects of other opioids, was not inhibited.^{172,173} The clinical effectiveness of buprenorphine in combination with bupivacaine has been reported in a 77-year-old woman who developed refractory nociceptive-neuropathic pain after a total hip arthroplasty. Mean daily doses of 37 mg bupivacaine and 0.114 mg buprenorphine administered intrathecally (for over 6 years) provided the patient with 85–100% pain relief.¹⁷⁴ In another evaluation, 21 patients were studied immediately after (nociceptive pain) and at 1 month (neuropathic pain) following thoracic surgery.

The analgesic dose of buprenorphine needed to reduce pain by 50% (the AD50) for postoperative nociceptive pain was compared to the AD50 for neuropathic pain. Neuropathic pain could be adequately controlled by buprenorphine; however, the AD50 for it was significantly higher than for nociceptive pain. Further, when the AD50 for nociceptive pain was low (e.g., 0.16 mg), the AD50 for neuropathic pain was 3 times higher (e.g., 0.5 mg). However, when the former was high (e.g., 0.6 mg), the latter was only slightly increased (e.g., 0.66 mg), showing that a large part of the difference seen in neuropathic pain was due to a pre-existing painful condition.¹⁶⁹ The authors concluded that postoperative neuropathic pain is treatable with opioids, treatment is dose responsive, and that dose responsiveness may be more reflective of individual differences and not of the neuropathic pain, *per se*.

Analgesic Supplemented Anesthesia. Buprenorphine has been used successfully as a supplement to anesthesia in dosages typically ranging from 5 to 40 $\mu\text{g}/\text{kg}$.¹⁷⁵⁻¹⁷⁷ In one of the trials,¹⁷⁷ one-half of the patients undergoing biliary surgery who received buprenorphine in dosages of 30 to 40 $\mu\text{g}/\text{kg}$ requested an analgesic within 5 minutes of extubation. Surprisingly, none of the patients receiving 10 to 20 $\mu\text{g}/\text{kg}$ needed an analgesic within 1 hour of the operation, although some required supplemental analgesics intraoperatively. Although a precise explanation for this phenomenon is lacking, and analgesic requests could have been related to sedation, nausea, or vomiting, all patients reportedly were awake or woke up when spoken to. The influence of nausea and vomiting during the first postoperative hour was apparently negligible. In a study of single-dose, buprenorphine-supplemented anesthesia in patients undergoing cholecystectomy, multiple regression techniques indicated that the duration of analgesia was dependent on the age of the patient, but not on the weight-adjusted dose of buprenorphine, nor the sex, or body weight of the patient.¹⁷⁸

In a comparison of intraoperative buprenorphine (0.6 mg) to methadone (20 mg) in women undergoing laparohysterectomy, those who received buprenorphine required fewer doses of supplemental analgesic and had a longer duration of analgesia.¹⁷⁹ Buprenorphine

(2 and 5 $\mu\text{g}/\text{kg}$) has also been compared to meperidine (0.8 mg/kg) for intraoperative use in balanced anesthesia.¹⁸⁰ Twenty percent of the patients in the buprenorphine group required analgesic supplementation compared to 40% in the meperidine group, although recovery was quicker in the meperidine group.

Drug Discrimination, Abuse Liability, and Physical Dependence

Drug Discrimination. Drug discrimination studies are often used to determine if the properties of a test drug are similar to those of a known (control) drug. In these types of investigations, an individual is trained to discriminate the control drug and is subsequently exposed to varying doses of the test drug to determine its generalization of effects compared to the control. The greater the generalization to the control drug of abuse, the greater the likelihood for abuse.

A 2- or 3-choice procedure has been utilized in clinical laboratory studies to assess an individual's ability to discriminate buprenorphine from no drug (saline placebo), a mu-opioid agonist (e.g., hydromorphone), or a mu-opioid mixed agonist-antagonist (e.g., butorphanol, pentazocine, nalbuphine). In the 2-choice procedure, the subject is trained to recognize 2 drugs, or 1 drug versus placebo (saline), whereas in the 3-choice procedure, the subject is trained to recognize 3 drugs, or 2 drugs versus placebo.

Using the 2-choice procedure, 3 opioid agonist-antagonists (pentazocine, butorphanol, nalbuphine) and the partial agonist buprenorphine were discriminated as hydromorphone-like.¹⁸¹ When varying doses of pentazocine and placebo were compared to varying doses of buprenorphine in a 3-choice procedure, buprenorphine was identified half the time as hydromorphone and half as pentazocine. No dose of buprenorphine generalized completely to pentazocine or hydromorphone.¹⁸² These studies demonstrated that, although buprenorphine may be discriminated as hydromorphone when the only choice is between hydromorphone and saline, it must also share some discriminative stimulus properties of pentazocine because buprenorphine has also been identified as that drug.

In a 3-choice procedure, buprenorphine produced a subjective effects profile similar to hydromorphone, whereas nalbuphine produced

a profile more similar to, and was identified as, butorphanol.¹⁸³ Pentazocine was not found to be similar to either butorphanol or hydromorphone. In a variation of the 3-choice procedure where individuals were trained to discriminate between high- and low-doses of hydromorphone, nalbuphine generalized to low-dose hydromorphone, whereas buprenorphine produced 75% responding (partial generalization) to low-dose and 25% responding (slight generalization) to high-dose hydromorphone.¹⁸⁴

The authors of the above two studies concluded that the effects observed with buprenorphine were consistent with a mu-opioid partial agonist because buprenorphine was discriminated as hydromorphone-like in both the 2- and 3-choice procedures. The observation that it was discriminated as both hydromorphone and pentazocine under a 3-choice procedure in which individuals were trained to discriminate pentazocine, hydromorphone, and saline can be explained by the fact that pentazocine has some mu-opioid-like activity. It can, therefore, be concluded from these studies that buprenorphine has a unique pharmacological profile that differs from mixed agonist-antagonists and that this profile is consistent with a mu-opioid partial agonist.

Abuse Liability. FDA Research Guidelines describe "abuse liability" as the "likelihood that a drug with psychoactive or central nervous system effects will sustain patterns of nonmedical self-administration that result in disruptive or undesirable consequences."¹⁸⁵ Psychoactive medications that produce elevations in the feeling of pleasure, euphoria, or mood may have potential for abuse. Individuals trained to recognize a mu agonist will identify buprenorphine as a mu agonist when it is the only choice they have. However, when these same individuals are exposed to a mixed agonist-antagonist, buprenorphine may be identified as a mixed agonist-antagonist and less often as a pure mu agonist. Taken together, these results indicate that buprenorphine likely has an abuse potential similar to the mixed agonist-antagonists. Buprenorphine appears to produce a maximal effect of euphoria similar to that of 20 mg of morphine/70 kg.¹⁸⁶ As the dose is increased, buprenorphine is associated with a plateau with regard to subjective and physiologic effects,^{33,187,188} unlike full mu-opioid agonists.

This ceiling effect may limit the abuse potential of buprenorphine.

Between 1994 and 2001, there have been 26 mentions of buprenorphine in the Drug Abuse Warning Network (DAWN) "Table of Estimates of Drug-Related Emergency Department Visits and Mentions."¹⁸⁹ There are a number of reports of buprenorphine abuse in the international literature; generally this abuse has been associated with ease of availability, lack of regulatory controls, and/or a decrease in availability of strong opioids. In the United States, buprenorphine is currently classified as a Schedule III substance under the Controlled Substance Act of 1970 and will be subject to regulatory controls appropriate to its abuse liability.

Physical Dependence. Buprenorphine has the capacity to produce physical dependence as assessed from behavioral and physiologic changes that occur following the withdrawal of the medication after prolonged administration of high (i.e., supra-analgesic) doses. The withdrawal syndrome has been associated mainly with reports of subjective discomfort but not autonomic signs. It has generally been reported to be mild to moderate in intensity (25% of the maximum possible withdrawal-scale score), and has appeared to follow the time course of short- as compared to long-acting opioids; namely, onset of 1 to 3 days, peak of 3 to 5 days, and duration of 8 to 10 days.^{190,191} Although the slow receptor dissociation of buprenorphine would suggest that its withdrawal syndrome would be more similar to long-acting opioids, other factors, such as elimination half-life and intrinsic activity, also influence the observed time course.

Further evidence of buprenorphine's capacity to produce physical dependence has been demonstrated using a naloxone or naltrexone challenge test.^{61,192} Qualitatively, the withdrawal syndrome observed in individuals maintained on high doses of buprenorphine is indistinguishable from that observed with a full mu-opioid agonist. However, quantitatively, the dose of naloxone or naltrexone needed to induce the withdrawal syndrome is 15 to 50 times greater than that required to precipitate withdrawal effects at a comparable dose of a full mu-opioid agonist. Results from these tests are consistent with buprenorphine being a partial agonist at the mu-opioid receptor with high affinity and low intrinsic activity.

Role of Buprenorphine in the Treatment of Depression, Schizophrenia, and Other Mental Disorders

The use of opioids for the treatment of depression and other psychiatric and behavioral disorders may date back to the earliest recognition of opium's therapeutic properties. However, concerns regarding the abuse potential and liability of dependence have limited therapeutic opioid use primarily to the areas of analgesia and opioid dependence. Studies have shown that buprenorphine may be effective for the treatment of depression¹⁹³⁻¹⁹⁶ in patients who are nonresponsive to conventional therapy.^{197,198} It is estimated that 10-30% of patients with major depressive symptoms are non-responsive to conventional therapy.¹⁹⁹ The antipsychotic effects of buprenorphine in the treatment of schizophrenia have also been evaluated and potential benefits have been observed.^{200,201}

The prevalence of major depression in chronic pain patients may exceed 20%²⁰² and the occurrence of depression in patients referred for pain symptoms has been reported to be as high as 80%.²⁰³ Buprenorphine could be a medication with potential utility in patients with a comorbid diagnosis of depression and pain; however, studies in this group of patients have not been reported.

Safety

Buprenorphine Alone

Buprenorphine is safe and well-tolerated when used as recommended for both analgesia (as demonstrated in over two decades of use) and for the treatment of opioid dependence; the current number of patients receiving treatment for opioid dependence is approaching 200,000 worldwide (personal communication; Chris Chapleo, PhD, Reckitt Benckiser, March 3, 2004). Preliminary data from a survey of 3,255 patients with chronic pain who had used a transdermal buprenorphine product available in Europe indicated that, although adverse events were similar to those observed with other opioids, the incidence was relatively low compared to these opioids.¹⁶² Long-term use of buprenorphine administered as a transdermal system (mean exposure time 234 days, range 1-609 days) in approximately 400 patients with

chronic pain in a clinical trial showed no unexpected safety concerns.¹⁶⁹

Adverse events associated with buprenorphine, when used for either analgesia or addiction treatment, have been typical of opioids in general. These include constipation, headache, nausea, vomiting, sweating and dizziness, as well as respiratory depression, and changes in blood pressure and heart rate.^{186,204-206} Buprenorphine, when given alone, can produce a dose-related increase in respiratory depression and sedation²⁰⁷⁻²¹⁰ to a maximal effect that is generally clinically nonsignificant. For example, although Gal and coworkers, utilizing a carbon dioxide rebreathing method, observed marked drowsiness and a 40-50% decrease in the slope of the carbon dioxide response following the administration of buprenorphine (0.3 mg/70 kg IV) to healthy volunteers, the authors did not report that any subjects were terminated from the trial for safety reasons, but did note (with reference to buprenorphine-induced sedation) that quiet sleep alone was previously reported to produce a 20% decrease in the slope of the carbon dioxide response.²⁰⁸ Additionally, Walsh and colleagues reported that buprenorphine (given at a maximum dose of 32 mg sublingually to volunteers who were opioid-experienced but not physically dependent on opioids) maximally reduced respiratory rate by about 4 breaths per minute and reduced oxygen saturation by about 3% from the placebo condition of 98%; respiratory depression did not require medical intervention.³³

One of the most recently reported investigations was a dose-ranging study involving 6 experienced opioid users without opioid dependence.²¹¹ The study was conducted single-blind, double-dummy, with buprenorphine administered by both the intravenous (0 to 16 mg) and sublingual (0 and 12 mg) routes. The main adverse effects reported were sedation, mild irritability, nausea, and itching; 1 subject was discontinued from the study after the 12 mg IV dose secondary to severe nausea. The authors concluded that there was a ceiling for cardiac and respiratory effects and that buprenorphine had a high safety margin when administered by the intravenous route in the absence of other drugs.

If an overdose of buprenorphine is suspected and significant respiratory depression is observed, standard intravenous doses of an opioid

antagonist (e.g., naloxone or nalmefene) will not be effective in reversing the respiratory depression. In fact, doses of naloxone hydrochloride as high as 10–35 mg/70 kg may be required.^{61,192} Buprenorphine is longer acting and binds more tightly to opioid receptors than naloxone or nalmefene. Thus, in cases of suspected buprenorphine overdose, the patient should be closely monitored and maintained with life support measures (e.g., artificial respiration), including multiple administrations of high-dose naloxone or nalmefene as needed to maintain respiration.

Dysphoric and psychotomimetic effects appear to be minimal, possibly because of the kappa antagonist properties of buprenorphine. It is possible for buprenorphine to precipitate an opioid abstinence syndrome in individuals heavily dependent on opioids. Therefore, buprenorphine should be given with caution to patients who are physically dependent on other opioids, and taking greater than or equal to the equivalent of 30 mg of oral methadone or 120 mg of parenteral morphine. The most serious adverse events, including death, have been reported when buprenorphine has been administered in combination with other CNS depressants, especially the benzodiazepines (see Buprenorphine Overdosage section, below). A number of studies have assessed subjective effects of buprenorphine in drug-non-abusing volunteers.^{210,212,213} Analgesic doses of buprenorphine were associated with significant psychomotor impairment and subjective changes compared with pre-buprenorphine baseline.^{212,213} Additionally, when administered intravenously, 0.3 mg of buprenorphine was associated with a greater magnitude of subjective and psychomotor impairing effects than an equianalgesic (10 mg) dose of morphine.²¹⁰ Compared to individuals maintained on a full agonist (e.g., methadone), individuals chronically maintained on buprenorphine appear to have less cognitive-motor impairment as measured by psychomotor performance and driving ability.²¹⁴ Increases in aminotransferase (AST and ALT) levels have been reported in clinical trials assessing buprenorphine for addiction treatment.^{204,215} Further, hepatotoxicity has been reported in large overdoses and individuals misusing buprenorphine parenterally^{216,217} and 53 cases of buprenorphine-associated cytolytic hepatitis have been reported in France

since buprenorphine was introduced as a treatment for opioid dependence in 1996.²¹⁸ However, adverse hepatic effects have not been reported for individuals receiving buprenorphine in analgesic dose ranges.

Buprenorphine Overdosage

Most reports of buprenorphine overdose have involved the inappropriate use (e.g., crushing and injection of sublingual preparations) of high-dose buprenorphine for the treatment of opioid dependence, and have occurred in combination with other central nervous system depressants (e.g., benzodiazepines). Reports from the United States have been limited primarily to those from clinical investigations. Effects have included respiratory depression (with a ceiling) at doses between 8 and 16 mg of the sublingual solution,³³ and severe nausea and vomiting following rapid intravenous buprenorphine infusion of 0.3 mg/70 kg.²¹⁹

There have been only a few case reports of buprenorphine (alone) overdoses outside the United States, and only 2 of these were fatal. The cause of death in these cases was ascribed to Mendelson's Syndrome (acute aspiration of gastric contents), with reported blood buprenorphine concentrations of 0.8 ng/mL and 3.1 ng/mL.²²⁰ Other reports included cases of cutaneous complications following injection of crushed tablets,²²¹ myocardial infarction following insufflation,²²² and respiratory depression^{211,223} in which individuals made a full recovery.

In France, buprenorphine is the predominant medication used to treat opioid dependence, with approximately 100,000 patients in treatment (personal communication; Chris Chapleo, PhD, Reckitt Benckiser, March 3, 2004). Primary care physicians prescribe buprenorphine with minimal regulatory restrictions. This wide availability and limited regulatory control has provided an opportunity to assess the overall safety of buprenorphine. There have been a number of reports of fatal overdoses associated with buprenorphine since its introduction in France for use in the treatment of opioid dependence.^{220,224,225} The report by Tracqui and coworkers²²⁵ totaled 20 fatalities. Another report described 117 buprenorphine-associated fatal overdoses between January 1996 and May 2000.²²⁰ All of these 137 reported cases associated with buprenorphine

recently have been reviewed.²²⁶ Most of these fatal overdoses were associated with the concomitant use of psychotropics or CNS depressants, especially benzodiazepines. The majority of these deaths occurred when buprenorphine tablets were crushed and injected intravenously along with another drug. An additional report compared the number of deaths associated with buprenorphine ($n = 27$) and methadone ($n = 19$) between 1994 and 1998.²²⁴ The low number of deaths reported by Auriacombe and colleagues probably reflects fewer patients in treatment for opioid dependence between 1994 to 1998 compared to 1996 to 2000.

Reversal of Buprenorphine Effects with Naloxone, Nalmefene, or Naltrexone

Currently, there are 2 (naloxone and nalmefene) opioid antagonists approved by the FDA for the treatment of acute opioid overdose. Naloxone was the first approved and is a short-acting antagonist with high affinity for the mu-opioid receptor. Naloxone reverses multiple actions of opioids, including respiratory depression. It is essentially without intrinsic activity, including respiratory or cardiovascular effects.²²⁷ When naloxone is administered to an opioid dependent person, it will precipitate an acute opioid withdrawal syndrome and will reverse signs and symptoms of acute opioid overdose, including respiratory depression, sedation, and hypotension. At doses of 0.4 to 0.8 mg given parenterally, it begins to reverse the manifestations of opioid overdosage within 2 minutes. Because naloxone competes with the opioid agonist for receptor binding sites, the dose required to treat overdosage depends on the opioid taken and the severity of intoxication. Larger doses may be necessary in certain circumstances (see Buprenorphine Alone section, above). The duration of naloxone action is between 1 and 4 hours depending on dose and route of administration. The difference in onset and duration of naloxone's actions on the respiratory depressant effect of buprenorphine compared to a mu-agonist (e.g., morphine) is striking. Studies have shown that naloxone doses ranging from 5 to 12 mg are required to reverse the respiratory depressant effects of buprenorphine in the analgesic therapeutic dose range.^{208,228,229} The effects of naloxone were delayed for 30 to 60 minutes and extended for up to 3 to 6 hours. Naloxone may

need to be given in repeated doses when treating an overdose induced by a long-acting opioid such as buprenorphine. Further, because of the short duration of naloxone effect, patients should be observed even after apparent recovery. No adverse effects of naloxone have been observed in cases of acute opioid intoxication, and parenteral doses of 24 mg/70 kg and oral doses as high as 3000 mg have been given without incident.²³⁰ However, in some cases, naloxone may not be effective in reversing the respiratory depression produced by buprenorphine. Thus, the primary management of overdose should be the reestablishment of adequate ventilation with mechanical assistance of respiration, if required.^{2,231}

Nalmefene is also approved to treat opioid overdose and for reversal of postoperative opioid effects. After intravenous administration, the onset of action is within 2 minutes and peak effect occurs in 5 minutes. Nalmefene and naloxone are equipotent, but nalmefene has a longer duration of action.²³² However, multiple doses may still be necessary.

Naltrexone is another mu-opioid antagonist. It is approved in the United States as an oral medication for the treatment of opioid and alcohol dependence. It is not approved for the treatment of opioid overdose, although there are reports of its utility for methadone overdose treatment.^{233,234} When compared to parenteral naloxone, oral naltrexone produced equivalent dose-dependent opioid-withdrawal effects in buprenorphine-maintained individuals.⁶¹

Buprenorphine with Medications Used Therapeutically

Increased respiratory and central nervous system depression may occur when buprenorphine, like other opioids, is combined with other CNS depressant medications. These medications may include other opioid analgesics, general anesthetics, various sedatives and hypnotics (including benzodiazepines), antihistamines, and other drugs.²³⁵⁻²³⁹ For example, in a study of 12 patients undergoing cholecystectomy, buprenorphine was administered preoperatively at a dose of either 30 or 40 $\mu\text{g}/\text{kg}$ intravenously.²⁴⁰ Pre- and intra-operative medications included diazepam, thiopentone, pancuronium, suxamethonium, and nitrous oxide. The respiratory rate fell below 8 breaths per minute in one-half of the patients 15 minutes

following buprenorphine administration. A significant decrease in arterial pH and increase in PaCO₂ were observed postoperatively in the 40 compared to 30 µg/kg group.

Clinically, buprenorphine functions as a potent mu-opioid agonist analgesic at low doses, but at high doses has been shown to have a maximal opioid effect that is less than would be expected of a full mu-opioid agonist. As a result, buprenorphine may precipitate a withdrawal syndrome in individuals who are highly tolerant to, and dependent on, other opioids.

It is unlikely, however, that buprenorphine will antagonize or reverse the agonist effects of chronically administered opioids at dosages equivalent to less than 120 mg/day of parenteral morphine, or 30 mg/day of oral methadone. In opioid-dependent individuals stabilized on 60 mg/day of intramuscularly given morphine, buprenorphine 2 mg (administered intravenously) failed to reverse morphine effects with regard to various physiologic, subjective, and observer-rated measures.^{241,242} Further, buprenorphine 6 mg (given intramuscularly) failed to antagonize morphine-associated effects in individuals treated chronically with intramuscular morphine in dosages of up to 120 mg/day.²⁴³ Similar studies have been conducted in individuals maintained on 30 and 60 mg of methadone daily^{209,244,245} and challenged with buprenorphine in the dose range of 0.5 to 8 mg (given intramuscularly) or 2 to 8 mg (given sublingually). At the 30 mg methadone dose level, buprenorphine was associated with opioid-withdrawal effects when administered 2 hours after the methadone dose but not when administered 20 hours after methadone dosing. At the 60 mg methadone dose level, buprenorphine was associated with opioid-withdrawal effects when administered 40 hours after the methadone dose. Thus, although buprenorphine may antagonize some of the effects of morphine or other opioid agonists, this potential effect is dependent on at least 3 factors: dose of buprenorphine, dose of the other opioid, and the time interval between the administration of the 2 medications.

It is important to note the possibility of a drug interaction between buprenorphine and certain HIV-1 protease inhibitors, especially because buprenorphine may be used in the management of AIDS-associated pain (and the treatment of opioid addiction) in individuals

receiving these inhibitors. As discussed earlier, buprenorphine is metabolized by cytochrome P-450 3A4. A study utilizing human liver microsomes indicated that ritonavir, indinavir, and saquinavir competitively inhibited the metabolism of buprenorphine;²⁴⁶ the most potent inhibitor was ritonavir. A recent investigation also gave a preliminary indication that the use of buprenorphine (at higher than analgesic doses) in HIV-infected drug users had no major, short-term influence on HIV viral load in individuals receiving highly active antiretroviral therapy.²⁴⁷

Although data are limited, there may also be a potential for a buprenorphine interaction with other drugs and compounds that induce or inhibit the cytochrome P-450 3A4 system. There are many agents in this category and they include erythromycin, zileuton, and grapefruit juice (inhibitors), as well as carbamazepine, phenobarbital, phenytoin, and rifampin (inducers). In an *in vitro* study of the effects of the selective serotonin reuptake inhibitors fluoxetine and fluvoxamine, the demethylated metabolite of fluoxetine (norfluoxetine) and fluvoxamine, but not fluoxetine, were both shown to inhibit buprenorphine dealkylation.²⁴⁸

Buprenorphine with Abused Drugs

Some of the therapeutic drugs that have the potential to interact with buprenorphine may also be used as drugs of abuse (e.g., opioids, benzodiazepines). When abused, these drugs are often used in larger amounts and for longer periods of time than when used therapeutically. The abuse or therapeutic use of buprenorphine in combination with drugs that are more often abused than used therapeutically, such as cocaine, could also raise concerns regarding a potential for increased toxic effects secondary to the combined use of both drugs. Interestingly, a preclinical study revealed that buprenorphine (0.3 to 3.0 mg/kg intraperitoneally) protected against the lethal effects of cocaine-induced convulsions in mice.²⁴⁹ Cocaine (75 mg intraperitoneally) produced convulsions in all mice and lethal convulsions in 75% of the animals. Buprenorphine pretreatment significantly attenuated lethality, even though cocaine-induced convulsions were equivalent in buprenorphine-treated and vehicle-pretreated mice. This effect appeared to be mediated by the mu-opioid agonist actions of buprenorphine

because pretreatment with low doses of intraperitoneal naltrexone (0.3 to 1.0 mg/kg) antagonized the protective effect of buprenorphine. Another preclinical evaluation using lower intraperitoneal doses of buprenorphine also indicated that buprenorphine pretreatment was associated with an increased LD₅₀ for cocaine in mice.²⁵⁰ Other studies in animals indicated that buprenorphine may enhance some effects of cocaine (e.g., turning in rats), whereas other effects may be attenuated.^{251–253}

A clinical laboratory evaluation assessed the safety of buprenorphine alone and in combination with cocaine and morphine.²⁵⁴ The physiological effects of a single-blind challenge dose of cocaine (30 mg), morphine (10 mg), and saline placebo, all given intravenously, were assessed before and during maintenance of patients on 4 or 8 mg daily of sublingual buprenorphine solution. This dosage of buprenorphine is higher than that used for analgesia but typical of dosages that have been used for opioid addiction treatment. Cardiovascular responses to cocaine and morphine were equivalent under buprenorphine-free and maintenance conditions. The same was observed for respiration and temperature changes in response to cocaine, and morphine was associated with nonstatistically significant lower respiratory rates. These data suggested that daily maintenance on buprenorphine was not associated with adverse effects or toxic interactions with single doses of intravenous cocaine or morphine.

Most of the deaths associated with buprenorphine exposure have been in combination with other drugs, and have been associated with high-dose sublingual tablets (those used for the treatment of opioid dependence) taken by various routes of administration, primarily massive oral or intravenous administration.²²⁶ A majority of the deceased individuals were reported to be addicts.^{220,225,255–258} Postmortem buprenorphine plasma concentrations were typically provided in the reports without an estimate of the buprenorphine dose ingested. Although in most cases buprenorphine concentrations in the blood were under 30 ng/mL, in one case a blood buprenorphine concentration of 3300 ng/mL was observed.²⁵⁸ The most frequently reported concomitant drugs found were benzodiazepines, including clorazepate dipotassium,

oxazepam, flunitrazepam, and diazepam; sometimes more than one benzodiazepine was reported. Other drugs found in combination with buprenorphine included morphine and ethanol. Although the precise role of the other drugs in combination with buprenorphine cannot be determined, their ability to produce respiratory depression suggested a pharmacodynamic interaction. While pharmacokinetic interactions cannot be ruled out, a study assessing the possible interaction of buprenorphine with flunitrazepam metabolism argues against a pharmacokinetic interaction.²⁵⁹ Although both compounds are metabolized by the cytochrome P-450 3A4, the estimated inhibition of buprenorphine N-dealkylation by flunitrazepam *in vivo* was only 0.08%, and the projected buprenorphine inhibition of flunitrazepam metabolism was 0.1–2.5%.

Factors Associated with Buprenorphine Abuse

The first published report of injectable buprenorphine abuse came from New Zealand.²⁶⁰ Buprenorphine abuse is more frequently observed in individuals already experienced in the use of heroin and other opioids. Buprenorphine is rarely the drug by which opioid abuse is initiated. Where buprenorphine abuse has been reported, buprenorphine is often obtainable at a lower cost, with easier availability, and with a higher and more consistent purity than heroin.^{261–265} Because of the extensive first-pass hepatic metabolism, abuse of buprenorphine by the oral route is unlikely. Buprenorphine solutions for parenteral administration would likely be the most desirable based on ease of administration. Buprenorphine tablets could be misused “as is” sublingually, but would require manipulation to effect them suitable for parenteral abuse. Buprenorphine in combination with naloxone apparently has less abuse potential than buprenorphine alone; buprenorphine with naloxone was reportedly less desirable to abusers than buprenorphine alone.¹⁴⁶ Buprenorphine and the buprenorphine/naloxone combination were approved for the treatment of opioid addiction in the United States in October 2002.¹⁴

The abuse liability of transdermal buprenorphine relative to other forms of buprenorphine

should be considered for 2 populations: 1) patients who use the medication as directed, and 2) substance abusers who may divert and/or misuse the product. When used as directed for analgesia, abuse of transdermal buprenorphine would be limited by the relatively low plasma concentrations achieved, and by the slow rise and fall of these concentrations. A study by Becker and colleagues indicated that transdermal buprenorphine resulted in fewer, less intense and delayed opioid effects, including objective effects (decreases in pupil diameter), subjective effects (general drug effect, drug liking, heroin feeling) and cognitive effects (digit symbol substitution tests), and thus a lower abuse potential than intramuscular buprenorphine.²⁶⁶ In fact, transdermal buprenorphine produced few significant differences from placebo. The potential that buprenorphine from the transdermal product will be abused by people with addictive disorders was not fully assessed by this study. Nonetheless, abuse of a transdermal product could occur through excessive use of the intact dosage form, through chewing or other methods of altering the dosage form to increase absorption, or through buprenorphine extracted from the system for the purpose of parenteral misuse. However, data from France, where buprenorphine is widely available from general practitioners as sublingual tablets for the treatment of opioid addiction, show a substantially lower death rate associated with buprenorphine compared with methadone.²²⁴ This is consistent with the wider margin of safety in overdose due to the partial agonist activity of buprenorphine.

Summary

Opioid analgesics are the primary therapeutic agents used for moderate to severe pain. In the past, clinicians have often been reluctant to prescribe opioids, especially in high doses. This reluctance was generally based on concern that an "addict" would be created through iatrogenically induced physical dependence. This concern is generally unfounded;²⁶⁷ rather, pseudoaddiction (an iatrogenic syndrome of abnormal behavior developing as a direct consequence of inadequate pain management) may be of more importance. Contributing factors include prescribing of less than adequate

doses of analgesics, increased demand for analgesics by the patient, and deterioration of the doctor-patient relationship.²⁶⁸

Chronic pain patients may be more difficult to manage than those in acute pain due to secondary medical and psychiatric disorders related not only to the disease but also to disease treatment. The goal in providing effective therapy should be to eliminate or reduce the pain, to improve the patient's quality of life, and to minimize medication side effects. These goals may be better achieved through the use of longer-acting medications or dosage forms that will provide for more stable analgesic plasma levels, increased patient compliance, and minimal adverse events, and that will also provide better pain control with less risk for physical and psychological dependence. The physiochemical characteristics and pharmacological profile of buprenorphine make it an excellent medication for the treatment of both acute and chronic pain utilizing a variety of different delivery systems, including the transdermal delivery system.

In man, the primary activity of buprenorphine is as a mu-opioid partial agonist and a kappa-opioid antagonist. Buprenorphine is indicated for the treatment of moderate to severe pain. It is not administered orally secondary to extensive first-pass metabolism. Typical dosages are 0.2 to 0.4 mg (sublingually) or 0.3 to 0.6 mg (parenterally) every six hours. A 72-hour transdermal product designed to continuously release buprenorphine at either 35, 52.5, or 70 µg/hr is available in Europe. Another transdermal formulation is under development in the United States. Buprenorphine has also been used by other routes of administration (e.g., intra-articular and for sympathetic nerve blocks).

Common side effects following buprenorphine administration may include sedation, nausea and/or vomiting, dizziness, and headache. Respiratory depression may occur and may not be responsive to treatment with naloxone; however, as a mu-opioid partial agonist with a demonstrated ceiling on respiratory depression, buprenorphine may have a better safety profile compared to full mu agonists.

Buprenorphine also has the potential to be abused and should be used cautiously in individuals with a past or current history of substance abuse or dependence. Buprenorphine

produces opioid-like subjective and physiologic effects. The level of effect is limited and dependent on the dose and route of administration. The greatest potential for abuse, however, may be through the diversion of buprenorphine into illicit channels. How significant this diversion may be will be dependent on numerous factors, including general medication availability, the amount of regulatory control over buprenorphine, and the general availability (or lack thereof) of other, more-preferred opioids. Overall, buprenorphine is a highly effective analgesic for the treatment of moderate to severe pain. It has a unique pharmacological and physiochemical profile allowing for relatively safe use, and flexibility with regard to dosage and dosage forms. Nonetheless, buprenorphine has not been as extensively studied in certain populations (e.g., in individuals suffering from pain of malignant origin) as other opioid analgesics and additional research is needed to better define the role for buprenorphine in various patient subpopulations.

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