David S. Warner, M.D., Editor

Buprenorphine–Naloxone Therapy in Pain Management

Kelly Yan Chen, B.S., Lucy Chen, M.D., Jianren Mao, M.D., Ph.D.

ABSTRACT

Buprenorphine–naloxone (bup/nal in 4:1 ratio; Suboxone®; Reckitt Benckiser Pharmaceuticals Incorporation, Richmond, VA) is approved by the Food and Drug Administration for outpatient office-based addiction treatment. In the past few years, bup/nal has been increasingly prescribed off-label for chronic pain management. The current data suggest that bup/nal may provide pain relief in patients with chronic pain with opioid dependence or addiction. However, the unique pharmacological profile of bup/nal confers it to be a weak analgesic that is unlikely to provide adequate pain relief for patients without opioid dependence or addiction. Possible mechanisms of pain relief by bup/nal therapy in opioid-dependent patients with chronic pain may include reversal of opioid-induced hyperalgesia and improvement in opioid tolerance and addiction. Additional studies are needed to assess the implication of bup/nal therapy in clinical anesthesia and perioperative pain management. **(ANESTHESIOLOGY 2014; 120:1262-74)**

CHRONIC pain lasting more than 3 to 6 months can affect anyone at any stage in life.[1] In 2010, 31% of the American population experienced chronic pain.[2] It is one of the most frequent reasons to seek medical care and a major public health problem for both individuals and the society. For centuries, opioids have been used for pain management and regarded as among the most powerful drugs for the treatment of chronic pain. When properly managed, opioid therapy is considered to improve patients' quality of life, decrease healthcare costs, and promote work productivity.

The increasing number of patients searching for pain relief during the last several decades has led pharmaceutical companies to develop a plethora of opioid medications. Unfortunately, this increase in the number of opioid medications and dispensing is correlated with an increase in opioid abuse.[3,4] According to a recent report, approximately 21 million people in the United States aged 12 and older have used prescription drugs for nonmedical reasons at least once in their lifetimes.[5] The increase in the nonmedical use of opioids is paralleled by the steady increase in the number of deaths from unintentional opioid overdoses. Since 2003, more deaths have been associated with opioid overdose than cocaine or heroin use combined.[6] In addition to the known side effects associated with the use of opioid analgesics, the nonmedical use of prescription opioids has made it much more difficult to achieve the goal of alleviating pain with opioid therapy without causing significant adverse consequences. This issue is further complicated by managing patients with both chronic pain and opioid dependence or addiction.

Buprenorphine–naloxone (bup/nal; Suboxone® [Reckitt Benckiser Pharmaceuticals Incorporation, Richmond, VA]) is a semisynthetic opioid. Although developed as an analgesic, bup/nal was popularized for its effectiveness in opioid-replacement therapy. With the increasing challenge of managing pain in opioid-dependent patients, bup/nal has been prescribed off-label for the treatment of chronic pain, whereas a consensus is yet to be reached with regard to its effectiveness. To assess the effectiveness of bup/nal therapy, it would be important to determine the effectiveness of bup/nal in at least three patient populations who (1) have opioid addiction but without chronic pain; (2) have chronic pain on high-dose opioids; and (3) are dependent on or addicted to opioids with coexisting chronic pain. In this article, we will (1) examine the effectiveness of bup/nal in these patient populations, (2) compare the effectiveness of bup/nal with that of methadone in pain management, (3) discuss implications of bup/nal therapy in clinical anesthesia and perioperative pain management, and (4) examine possible mechanisms of bup/nal therapy in pain management.

Materials and Methods

We aimed for an integrative summary of the current knowledge on the effectiveness of using bup/nal for pain management. A computerized literature search in PubMed and Google Scholar was conducted between June 10, 2013 and August 2, 2013,

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which included the available literature up to that point. The following keywords and their combinations were used in both searches: suboxone, buprenorphine–naloxone, buprenorphine, naloxone, subutex, chronic pain, pain management, opioid dependent, office-based addiction, methadone, pharmacology, opioid-induced hyperalgesia (OIH), opioid naive, and buprenorphine history. This search included review articles, prospective and retrospective clinical studies, editorials, and comments. We also searched for relevant articles by using those keywords in the reference lists from the retrieved journals. No time restraint was placed on the literature search, but the search results indicate that all of the clinical trials relating bup/nal to pain management were conducted from 2002 and onwards. Studies were included if they specify buprenorphine or bup/nal as the primary pharmacological agent used for either opioid management or pain management. Studies that compared bup/nal therapy to other opioids in terms of pain management or opioid management were also included. In analyzing the published articles and organizing this review, we recognized that the literature pool on this topic is still relatively small that may not be appropriate for us to construct a traditional systematic review with the rating on the published articles. Instead, we consider this article as a topical review with a combination of up-to-date references and comments on the relevance to the topic under review. These comments are included in the main text and in four tables.

Historic Perspectives

After decades of research and many failed attempts, Reckitt & Colman Research Lab (now Reckitt Benckiser Pharmaceuticals) in England synthesized buprenorphine in 1966. With high enthusiasm for the drug, the intravenous form of buprenorphine became available in 1978. Soon after, in 1982, a sublingual version of buprenorphine became available for analgesia. In 1985, buprenorphine was introduced into the United States as an opioid analgesic.[7] To date, buprenorphine is formulated in two forms. The initial form contains only buprenorphine (*e.g.*, Subutex®; Reckitt Benckiser Pharmaceuticals Incorporation). Similar to other opioids, buprenorphine has the potential to be intravenously abused as shown by an increasing record of abuse in many countries.[8] To address this issue, naloxone (an opioid receptor antagonist) was added to buprenorphine and this buprenorphine–naloxone (bup/nal) combination drug was trademarked as Suboxone®. Although Subutex® and Suboxone® both contain buprenorphine as its main ingredient, the addition of naloxone to buprenorphine pharmacologically distinguishes bup/nal from buprenorphine due to the opioid-antagonizing effect of naloxone.

In 2000, the U.S. Drug Addiction Treatment Act made it legal to prescribe schedule III, IV, V drugs to manage addiction and placed the limit of the number of patients on maintenance therapy to 100 patients under a single physician.* In 2002, the U.S. Food and Drug Administration approved bup/nal for office-based addiction treatment by categorizing it as a schedule III drug.[7] Later in 2007, the World Health Organization recognized buprenorphine and bup/nal as a treatment for opioid dependence by including both drugs in the 15th World Health Organization Model List of Essential Medicines, and both drugs have been on the list ever since.†‡§ By 2011, there had been 7.69 million buprenorphine-related prescriptions dispensed in the United States alone, with the majority of it being bup/nal.‖

Pharmacological Profile of Bup/Nal

Characteristics of Buprenorphine. Buprenorphine is a semisynthetic opioid as a derivative of thebaine, a naturally occurring opium alkaloid of *Papaver somniferum*. It has several interesting pharmacological characteristics that account for its unique mechanism of action. First, buprenorphine has a high binding affinity to the μ-opioid receptor, effectively competing with other opioids that bind to the same receptor (fig. 1). Second, buprenorphine functions as a partial μ-opioid receptor agonist (fig. 1). When buprenorphine binds to the μ-opioid receptor, it mimics the pharmacological effect of an opioid but to a much lesser extent, thus preventing opioid withdrawal symptoms. Third, buprenorphine has a slow rate of dissociation from the μ-opioid receptor,

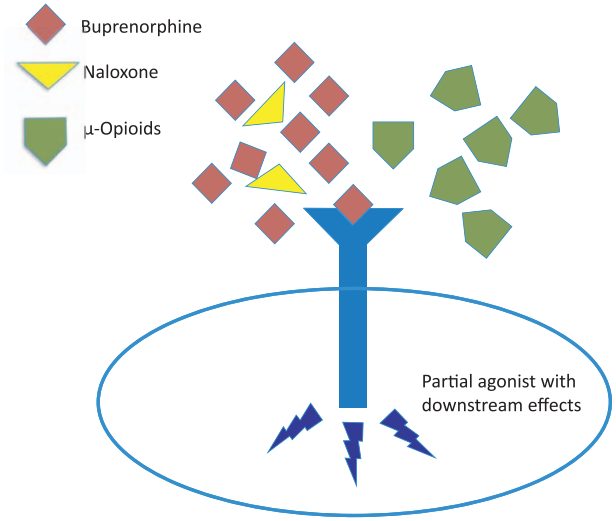

Fig. 1. Schematic illustration of the effect of buprenorphine as a partial μ-opioid receptor agonist.

* U.S. Department of Health and Human Services. Available at: http://buprenorphine.samhsa.gov/data.html. Accessed August 1, 2013.

† World Health Organization: WHO Model List of Essential Medicines. 2007. Available at: http://whqlibdoc.who.int/hq/2007/a95075_eng.pdf. Accessed July 1, 2013.

‡ World Health Organization: WHO Model List of Essential Medicine. 2010. Available at: http://whqlibdoc.who.int/hq/2011/a95053_eng.pdf. Accessed July 1, 2013.

§ World Health Organization: WHO Model List of Essential Medicine. 2011. Available at: http://whqlibdoc.who.int/hq/2010/a95060_eng.pdf. Accessed July 1, 2013.

‖ Drug Enforcement Administration. Available at: http://www.deadiversion.usdoj.gov/drug_chem_info/buprenorphine.pdf. Accessed August 1, 2013.

producing a prolonged duration of action as compared with other opioids.[9,10] Fourth, buprenorphine is also a full κ-opioid receptor antagonist. Activation of the κ-opioid receptor contributes to the opioid's dysphoric and psychotomimetic effects, which could be diminished by buprenorphine.[11–13] Fifth, buprenorphine has a large volume of distribution and is highly protein bound (96%), primarily to α- and β-globin.[14] Buprenorphine reaches its peak plasma concentration 90 min after administration and is extensively metabolized through 14-*N*-dealkylation by the hepatic CYP3A4 (primary pathway), CYP2C8, and CYP2C9 system to norbuprenorphine. Both buprenorphine and norbuprenorphine can then undergo glucuronidation by the uridine 5'-diphospho glucuronosyl transferases to form conjugated byproducts.[15,16]# These glucuroconjugated metabolites are then eliminated mainly in feces by biliary excretion 4 to 6 days after administration with minimal urinary excretion.[16] Early studies have shown that in mouse, buprenorphine can be 25 to 40 times more potent than morphine if given a parenteral injection and 7 to 10 times more potent after an oral administration and is longer acting.[9,17]

Characteristics of Naloxone. Naloxone is a short-acting, broad opioid receptor antagonist. It binds to opioid receptors with high affinity and becomes a competitive antagonist of opioid receptors (fig. 2). When administered at low doses, naloxone can reverse opioid side effects such as respiratory depression, sedation, and hypotension without significantly reversing analgesia. At high doses, however, naloxone can block opioid analgesia causing precipitated opioid withdrawal.[18] Naloxone is approximately 45% protein bound, primarily to albumin. It is rapidly metabolized by glucuronidation to naloxone-3-glucuronide in the liver and is primarily excreted in urine.**

Characteristics of Bup/Nal. Bup/nal is a sublingual combination tablet composed of buprenorphine and naloxone in a fixed 4:1 ratio. The fixed ratio was based on the need to maintain the therapeutic effect of buprenorphine while minimizing the antagonist effect of naloxone. Naloxone has no major clinical effect when administered sublingually and has a minimal impact on the pharmacological effect of buprenorphine for two reasons. First, there is a substantial difference in sublingual bioavailability of these two drugs. When administered sublingually, the bioavailability of buprenorphine (40%) is much higher than that of naloxone (10%) so that buprenorphine will exert the predominate effect.[19] Second, buprenorphine has 10 times longer duration of action (966 min) than that of naloxone (105 min) in the intravenous form.[9,14,17] As such, adding naloxone to buprenorphine could prevent intravenous abuse of buprenorphine because the bioavailability of naloxone increases when bup/nal is injected intravenously and its antagonist effect will render this combination drug undesirable for intravenous drug users.[14]

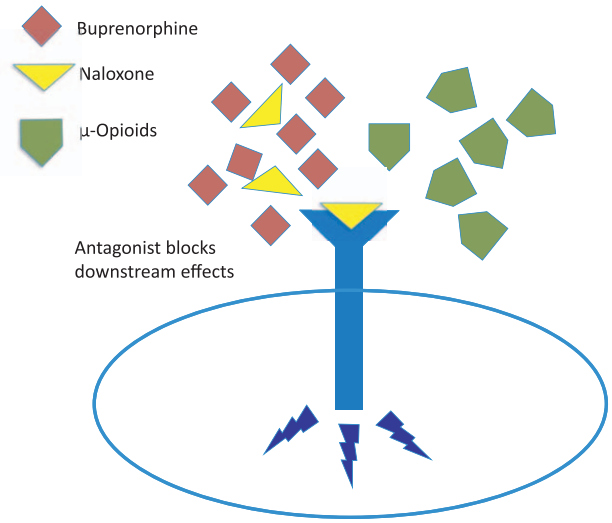

Fig. 2. Schematic illustration of the antagonizing effect of naloxone, an element in buprenorphine–naloxone, on μ-opioid receptors.

Adverse Effects of Bup/Nal

Despite a favorable pharmacological profile of bup/nal, bup/nal does have a number of adverse effects mainly through drug–drug interactions. Similar to other opioids, some typical side effects of bup/nal include nausea, dizziness, vomiting, and other symptoms. However, because buprenorphine is metabolized by the CYP3A4 system, it interacts with many drugs that are also cleared through this same P450 system. A serious and fatal drug interaction can occur in individuals who are concurrently taking buprenorphine with benzodiazepines (*e.g.*, diazepam or flunitrazepam). Benzodiazepines are also cleared by the hepatic P450 system and can lead to accumulation of drug metabolites. Other drugs that can affect the P450 system include antifungals (*e.g.*, fluconazole), antibiotics (*e.g.*, clarithromycin), and antidepressants (*e.g.*, fluoxetine) and should be avoided these drugs when taking buprenorphine.

Bup/Nal versus *Buprenorphine Alone*

A main pharmacological difference between buprenorphine and bup/nal is that the latter has naloxone added to buprenorphine. Studies have shown that the pharmacological effect of buprenorphine seems to be different in the form of bup/nal. For example, buprenorphine has a slightly higher sublingual bioavailability in bup/nal compared with the sublingual bioavailability in buprenorphine alone.[20] The addition of naloxone might also attenuate the acute effect of buprenorphine despite a low sublingual bioavailability of naloxone.[21] Moreover, when switched from buprenorphine to bup/nal in opioid-dependent patients, 50% of subjects in one study

European Medicine Agency: Summary of Product Characteristics. 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000697/WC500058505.pdf. Accessed July 1, 2013.

** Reckitt Benckiser Pharmaceuticals Incorporation. Available at: http://www.suboxone.com/pdfs/suboxonePI.pdf. Accessed July 1, 2013.

experienced adverse reactions that were absent before the switch, suggesting that these two drugs could have different pharmacodynamic profiles.[22] In another study, approximately 80% of opioid-dependent subjects who switched from buprenorphine to bup/nal had a "bad" experience and fewer than 20% of them felt that the two drugs were similar.[23] In yet another study, 54% of opioid-dependent subjects preferred the tablet size, taste, and sublingual dissociation time of bup/nal as compared with buprenorphine.[24] Collectively, these studies suggest that adding naloxone to buprenorphine may have pharmacologically transformed buprenorphine to be distinctly different from buprenorphine as a mono drug.

Bup/Nal for Outpatient Office-based Opioid Addiction Treatment

Since 1949, methadone has been the standard treatment for opioid addiction. However, methadone maintenance therapy has strict enrollment requirements and complex regimens that often leave many patients unable to receive treatment. In 1998, a few years before the approval of bup/nal, only 115,000 (19%) of the estimated 600,000 opioid-dependent patients at the time were enrolled in methadone maintenance programs.[25] In comparison, bup/nal seems to offer several advantages over methadone maintenance therapy. For instance, the unique pharmacological profile of bup/nal (1) diminishes the risk of respiratory depression from buprenorphine overdose, (2) produces only mild withdrawal symptoms even on abrupt termination, and (3) provides a better safety margin for office-based practices.[12] The approval of bup/nal for outpatient office-based treatment for opioid addiction was also aimed at improving access to addiction management for underserved communities and allow individuals who are not in methadone maintenance therapy to have access to addiction treatment. In order for physicians to prescribe bup/nal for office-based therapy, an application to the Department of Health and Human Services is required to obtain a waiver. To obtain a waiver, a certified Doctor of Medicine or Doctor of Osteopathic Medicine must undergo 8 h of bup/nal therapy training.††

To date, a number of studies have focused on the efficacy of bup/nal as an outpatient office-based treatment for opioid addiction (table 1). It has been shown that patients addicted to opioids can be safely treated in a primary care setting with limited resources and that the success rates were similar to those from specialized treatment centers using methadone.[26] Furthermore, there are potential economic advantages for treating clinically stable opioid-dependent patients with office-based bup/nal therapy. In a study that analyzed the cost effectiveness of treating patients with bup/nal (compared with no treatment) by using the monthly cost of bup/nal in 2010 against the improvement in the quality of life of the patient, they found that bup/nal maintenance therapy has a cost-effective ratio of $35,100/Quality-Adjusted Life Years and has 64% chance of being below the $100,000/Quality-Adjusted Life Years threshold as compared with no treatment.[27] The ratio shows the cost of bup/nal therapy to patients for every year of improved quality of life from the therapy. Current interventions with a cost-effectiveness ratio below $100,000/Quality-Adjusted Life Years are considered to be a good value in the United States.[27] In addition to being cost effective, patients are generally satisfied with bup/nal (rating 4.4 of 5) and those (40%) who were abstinent from illicit drug use in the first 6 months remained in maintenance treatment for an additional 2 yr.[28,29] Patients under bup/nal therapy were more likely to report abstinence (as compared with those not on bup/nal therapy), be involved in a 12-step recovery, be employed, and have improved psychosocial functional status (*e.g.*, "less likely to be unhappy," "have negative personality changes," or "do regretful things, and hurt family").[30] Collectively, these studies demonstrate the efficacy of bup/nal in office-based treatment for opioid addiction.

Bup/Nal as an Opioid Maintenance Therapy

In recent years, the increasing use of prescription opioids has been associated with a steady increase in prescription drug abuse and opioid-related death.[3,4] The unique pharmacological profile of bup/nal as a partial μ-agonist and full κ-antagonist in a fixed ratio with naloxone suggests that it could be used in opioid maintenance therapy. Maintenance therapy is a primary pharmacological approach to managing opioid dependence, which involves "replacement of abused opioids with medically prescribed opioids that are slow in onset, long acting, and less likely to be abused."[31] A number of studies have shown potential benefits of using bup/nal in patients who are dependent on opioids but without chronic pain (table 1). In a clinical trial, subjects on buprenorphine or bup/nal had more negative urinary samples for opioids, 40% less craving for opioids, and improved overall health status as compared with those on placebo.[32] However, it remains unclear as to whether bup/nal maintenance therapy is superior to methadone maintenance therapy, which has been the standard of care for opioid-addicted patients. Some studies have shown that bup/nal is as effective as methadone in producing negative urine samples for opioids and can be used as an alternative to methadone maintenance therapy.[33,34] At least one study suggests that bup/nal might be even more effective than methadone in reducing opioid consumption and preserving cognitive function.[35] Other studies suggest that methadone is more effective than bup/nal in reducing opioid use and retaining patients in the maintenance therapy.[36]

Several properties of bup/nal as a maintenance therapy are related to its unique pharmacologic profile. For example, the partial agonist activity of bup/nal can limit its therapeutic efficacy to a daily dose of 24 or 32 mg, which is equivalent to 60 to 70 mg methadone per day. Because many opioid-addicted patients were often placed on a much higher methadone

†† Drug and Treatment Act of 2000. Available at: http://buprenorphine.samhsa.gov/waiver_qualifications.html. Accessed August 1, 2013.

Table 1. Clinical Data on Bup/Nal as an Outpatient Office-based Addiction Treatment

Reference	Drug Dose and Study Duration	Type of Study	Treatment Regimen	Clinical Outcome	Comments
Fudala *et al.*[32] 2003	16 mg bup/nal daily for 4 wk	Randomized, double-blind clinical trial (n = 326) comparing bup/nal to buprenorphine and placebo	All subjects received HIV counseling and had up to 1 h of individualized counseling per week	Bup/nal or buprenorphine subjects showed reduced opioid use and craving for opioids during the study; a greater percentage of urine samples were negative for opioids in the bup/nal (17.8%) or buprenorphine (20.7%) group	*Strength:* This was a premier study addressing the effectiveness of bup/nal in an office-based setting *Limitation:* The trial ended early due to the overwhelmingly positive response to buprenorphine and bup/nal therapy
Barry *et al.*[28] 2007	Bup/nal therapy for 12 wk	Randomized, clinical trial (n = 142) comparing three treatment conditions, varying in counseling intensity (20 *vs.* 45 min) and medication dispensing (once weekly *vs.* three times weekly)	Bup/nal treatment with counseling with physician or nurse	Subjects were satisfied with primary care office-based bup/nal therapy; with an overall score of 4.4 of 5	*Strength:* The patient satisfaction questionnaire contained 19 questions, allowing for a wide range of response *Limitation:* A lot of study questions involved patient–healthcare provider interactions with a low external validity
Mintzer *et al.*[26] 2007	Individualized dose ranging from 8 to 24 mg bup/nal daily	Prospective, observational cohort study (n = 99)	Bup/nal treatment; subjects also attended alcoholics anonymous, narcotics anonymous, and/or counseling services	In total, 54% of subjects were sober at 6 mo. Opioid-addicted subjects were safely and effectively treated in a primary care setting with limited resources	*Strength:* The study was conducted in an urban environment with proper randomization of study subjects *Limitation:* Lack of an untreated control group
Fiellin *et al.*[29] 2008	Individualized dose ranging from 16 to 24 mg bup/nal daily for at least 2 yr	Prospective observational study (n = 53)	Bup/nal treatment with monthly counseling with a physician; patients with illicit drug use were provided with enhanced services	High subject satisfaction (86 of 95); 91% of the monthly urine specimen collected were negative for opioid. There was a moderate level of retention in primary care office-based treatment for addiction	*Strength:* The study followed patients up to 5 yr *Limitation:* A large number of patients, approximately 50%, had left treatment after 1 yr and they were not included in follow-up
Rapeli *et al.*[35] 2007	Mean daily bup/nal dose of 15.8 mg for 6 wk	Randomized clinical trial (n = 50) comparing bup/nal to methadone and placebo	Cognitive, attention, and memory tests were conducted	Bup/nal was more effective than methadone in the preservation of cognitive function within the 6 wk of the study	*Strength:* Included cognitive testing and two of three cognitive tests used a computer test, reducing the possibility of researcher bias *Limitation:* Cognitive tests were not fully validated
Kamien *et al.*[33] 2008	8 or 16 mg bup/nal daily for 17 wk	Randomized, double-blind clinical trial (n = 268) comparing bup/nal to methadone in varying dose strength	Subjects received 1 h of individual behavioral counseling with a therapist. Subjects were allowed to continue illicit drugs	Bup/nal was just as effective as methadone in producing positive outcomes (10% of 8 mg bup/nal, 17% of 16 mg bup/nal, 12% of 45 mg methadone, and 17% of 90 mg methadone had opioid negative urine samples for 12 consecutive urine samples. Urine sample were measured three times a week)	*Strengths:* The first clinical trial to compare the effectiveness between bup/nal and methadone as maintenance therapy; no take home therapy, reducing bias on the amount of drug taken; a double-blind and double-dummy design *Limitation:* Required participants to go to clinic every day to get medication, a possible confounding factor of study compliance

(*Continued*)

Table 1. *(Continued)*

Reference	Drug Dose and Study Duration	Type of Study	Treatment Regimen	Clinical Outcome	Comments
Parran *et al.*[30] 2010	Either 12 or 16 mg bup/nal daily for 18 mo	Retrospective chart review and cross sectional telephone interview (n = 176)	Full adherence was required. Those with substance abuse were referred back to the next highest level of care	Bup/nal was found to be a viable office-based opioid treatment option; 77% subjects were more likely to report abstinence, affiliated with 12-step recovery, be employed, and have improved functional status at the 18th month follow-up	*Strength:* The study explored the impact of socioeconomic status of patients on a bup/nal therapy *Limitation:* Patients had to follow through with every step of the bup/nal treatment or they would be discharged from the program
Schackman *et al.*[27] 2012	8 mg bup/nal daily for 2 yr	Prospective observational cohort study (n = 53)	Patients were allowed to continue on their illicit drugs	Bup/nal maintenance therapy had a cost-effective ratio of $35,100/QALY and has 64% chance of being below the $100,000/QALY threshold as compared with no treatment	*Strength:* Data were calculated from a cohort study and the quality of life weights were obtained from a clinical trial questionnaire *Limitation:* Did not consider the impact of bup/nal on other health services (*e.g.*, mental health services, decrease in criminal behaviors, *etc.*)
Neumann *et al.*[36] 2013	Individualized dose ranging from 4 to 16 mg bup/nal daily (mean: 14.9 mg) for 6 mo	Randomized open-label clinical trial (n = 54) comparing bup/nal to methadone	Subjects stopped self-administering opioid medications and illicit drugs and drinking alcohol. Nonopioid analgesics were allowed; and patients were encouraged to attend self-help programs	26 (48.1%) subjects noted a 12.8% reduction in pain score under bup/nal or methadone at the 6-mo follow-up. No subjects in the methadone group, as compared with five in the bup/nal group, reported illicit opioid use at the 6-mo follow-up	*Strength:* Approximately 50% of participants completed the study *Limitation:* An open-label design

Bup/nal = buprenorphine–naloxone; HIV = human immunodeficiency virus; QALY = Quality-Adjusted Life Years.

maintenance dose (usually 80 to 150 mg of methadone per day), bup/nal might not be as effective in such patients.[37] Nonetheless, with a lower abuse potential due to the addition of naloxone, a safety profile due to its ceiling effects and fewer withdrawal symptoms upon discontinuation and fewer respiratory depression complications than other opioids, bup/nal may be considered as a first-line medication for those who just begin opioid-dependence treatments.[12,17]

Rationales for Using Bup/Nal in Pain Management

In 2000, the American Pain Society and the American Academy of Pain Medicine published statements supporting the use of opioid therapy in patients with chronic pain. However, opioid medications are addictive and can cause adverse social, financial, mental, and economic consequences. Studies have shown that up to 45% of patients with chronic pain on opioid therapy reported aberrant drug-related behaviors. These behaviors include the use of alternative routes of administration of oral formulations, concurrent use of alcohol or illicit drugs, and the repeated usage of opioid therapy despite adverse effects.[38] Given that buprenorphine is regarded as an analgesic with a low addictive potential, sublingual buprenorphine and bup/nal have become increasingly prescribed off-label for the treatment of chronic pain based on the following considerations.[39] First, opioid dependence and addiction is an issue in many patients with chronic pain on opioid therapy. Patients with chronic pain are often prescribed with opioid medications that are subject to addiction and abuse. Second, patients on high-dose opioids often require alternative treatment for pain relief due to opioid tolerance and/or OIH.[40,41] Third, for those patients on high-dose opioids for chronic pain management, bup/nal could help taper these patients off, or lower, their dose of opioids. Despite these compelling reasons, a consensus is yet to be reached regarding the effectiveness of bup/nal therapy for patients with chronic pain as discussed in the following paragraphs.

Bup/Nal Therapy in Patients with Pain without Opioid Dependence

To our knowledge, there are currently no published studies that show the effectiveness of bup/nal for pain relief in non–opioid-dependent patients with chronic pain. This may not be surprising given that buprenorphine is a weak analgesic.

In low doses, buprenorphine can only partially activate the μ-opioid receptor. In moderate doses, the buprenorphine's opioid agonist effect reaches a plateau (ceiling) such that any further dose increase is unlikely to enhance analgesia. In high doses, buprenorphine functions as an opioid antagonist to further limit its analgesic effect.[42] Thus, the weak analgesic effect of buprenorphine in the form of bup/nal is unlikely to provide adequate pain relief for patients without opioid dependence or addiction.

Bup/Nal Therapy in Patients with Pain with Opioid Dependence

Patients with chronic pain with a coexisting substance abuse disorder are among the most challenging patients to manage. Effective pain management in this patient population is often complicated by opioid tolerance including cross-tolerance to various opioids and OIH. Bup/nal may have advantages over other opioids in this patient population because of its low addictive potential and partial μ-opioid receptor agonist activities. Indeed, an increasing number of studies support the concept of using bup/nal in opioid-dependent patients with chronic pain (table 2).

In one study, patients with chronic pain who converted from a full-agonist opioid therapy to a bup/nal therapy experienced a 2.3-point pain reduction (0 to 10 pain scale) within 60 days of the switch.[43] A retrospective chart review study conducted in a primary care setting also found that most patients with both nonmalignant chronic pain and opioid dependence who stayed on a bup/nal therapy showed a reduced pain level and required lower doses of bup/nal over time, and those who completed a bup/nal therapy were no longer taking any opioids.[44] Additional evidence is provided by several randomized clinical trials showing that (1) patients with chronic pain with opioid dependence experienced a 12.7% reduction in pain with a bup/nal therapy[36] and (2) bup/nal therapy reduced pain, opioid withdrawal symptoms, and opioid abuse in patients with chronic pain who were abusing oxycodone.[45] Collectively, the current data appear to support a role for bup/nal therapy in patients with chronic pain with opioid dependence or addiction.

Possible Mechanisms of Bup/Nal Therapy in Patients with Pain with Opioid Dependence

Although clinical data support a role of bup/nal therapy in patients with chronic pain with opioid dependence,

Table 2. Clinical Data on Bup/Nal Therapy in Patients with Pain with Opioid Dependence

Reference	Drug Dose and Study Duration	Type of Study	Clinical Condition	Concurrent Treatment	Clinical Outcome	Comments
Daitch *et al.*[43] 2012	A maximum of 32 mg of bup/nal daily in divided doses for 60 d	Retrospective observational study (n = 104)	Poorly controlled chronic pain despite short- and long-acting opioid analgesics	Subjects were allowed to switch back to previous opioids and still be included in the study	Mean pain score was decreased by 2.3 points on a 1–10 scale after 60 d	*Strength:* Participants' previous use of opioids were converted to morphine equivalents for better pain management and therapy comparison *Limitation:* This was a chart review study without a control group
Pade *et al.*[44] 2012	Individualized dose based on previous opioid use with a maximum of 28 mg bup/nal daily (mean = 16 mg; from 6 to 28 mg) with a variable treatment period	Retrospective chart review (n = 143)	Mixed chronic musculoskeletal and/or neuropathic pain	For subjects with psychiatric disorders, supportive and pharmacotherapy were added	Average pain score was decreased; 86% of subjects who stopped bup/nal required lower doses of initial opioid, whereas 14% were no longer taking any opioid	*Strength:* Used a very stringent monitoring protocol for subjects participating in the study *Limitation:* Although there were positive responses from patients, there was no control group
Roux *et al.*[45] 2013	On 2, 8, or 16 mg bup/nal daily (in random order) for 7 wk	Randomized clinical trial (n = 25) comparing bup/nal in varying doses with placebo	Chronic, nonmalignant pain with opioid dependence	Additional medications were allowed for emergent withdrawal treatment, if present	Reduction in pain, opioid withdrawal symptoms, and abuse liability of oral oxycodone during the 7-wk study	*Strength:* Subjects were admitted into an inpatient unit to fully transit their baseline opioids to bup/nal *Limitation:* Participants were given an option to accept $20 or a dose of oxycodone for pain. The participation could possibly be influenced by a socioeconomic background. The study also excluded participants with severe opioid dependence

Bup/nal = buprenorphine–naloxone.

the cause of pain relief in this patient population remains unclear. To date, most studies have focused on examining the effectiveness of bup/nal in pain management, but few have explored its underlying mechanisms. Does pain relief by bup/nal in this patient population result from reversal of OIH and/or opioid tolerance that are often associated with high-dose opioid therapy?[40,41] Does improvement of opioid dependence or addiction itself after bup/nal therapy lead to better pain relief in this patient population?

Several recent studies may shed some light on the possible mechanism of pain relief by bup/nal therapy. It has been shown that buprenorphine is an antinociceptive, although weak, by activation of the μ-opioid receptor.[9,46] In human subjects, buprenorphine exerts an antihyperalgesic effect and this effect has a longer half time than its analgesic effects.[47] Buprenorphine has been shown to reverse hyperalgesia induced by opioids through "buprenorphine-induced antinociception."[47,48] Moreover, buprenorphine is a κ-receptor antagonist and can compete with the effect of spinal dynorphin, an endogenous κ-receptor agonist. Because spinal dynorphin is increased after opioid exposure and contributes to OIH,[49] this competitive effect of buprenorphine on the κ-receptor binding site may decrease the effect of spinal dynorphin resulting in the decreased OIH.[50] Thus, reversing OIH might be a potential mechanism by which bup/nal therapy produces pain relief in patients with chronic pain with opioid dependence. Future studies are expected to examine whether pain relief by bup/nal in this patient population could also result from its effect on opioid tolerance and addiction.

Buprenorphine Alone in Patients with Pain without Opioid Dependence

Buprenorphine is often considered a second-line therapy for pain management because of its weak partial agonist activity. Most studies using buprenorphine alone have focused on the transdermal administration because of its high lipophilic properties. To date, there has not been a consensus as to whether buprenorphine alone would be an effective treatment in opioid-naive patients (table 3). One study showed that transdermal buprenorphine significantly alleviated chronic back pain in opioid-naive patients. But this decrease in pain became statistically nonsignificant when those patients who discontinued treatment were included as nonresponders.[51] Similarly, other studies have shown that transdermal buprenorphine was effective in reducing nonmalignant persistent pain, but it was only effective in 11% of the study subjects.[52] In that same study, 41% of patients on transdermal buprenorphine had discontinued the treatment due to unacceptable side effects or inadequate pain relief.[52] Other studies showed that patients on transdermal buprenorphine patches had improvement in their quality of life but with only moderate pain reduction.[53] Another study found similar results where buprenorphine was able to improve the overall wellbeing of patients suffering from osteoarthritis by improving sleep and movement abilities, but it did not reduce pain for these patients.[54] However, other studies showed that buprenorphine was able to alleviate pain in patients with cancer and can improve quality of life in these patients.[55] Overall, the exact role of buprenorphine in patients with chronic pain without opioid dependence remains to be investigated in future studies.

Buprenorphine Alone in Patients with Pain with Opioid Dependence

Similar to bup/nal, buprenorphine alone has been shown to alleviate pain in opioid-dependent patients (table 4). Patients treated with transdermal buprenorphine showed good or complete pain relief, improved duration of sleep, improved quality of life, and reduced need for additional sublingual buprenorphine.[56,57] A postmarketing surveillance study produced similar results on the effectiveness of transdermal buprenorphine in opioid-dependent patients with chronic pain who had inadequate analgesia from other opioids, showing that approximately 80% of the participants reported good pain relief and 70% of them moved onto a bup/nal therapy.[58] In addition, clinical studies, including a randomized clinical trial, have shown that substantial pain relief (66 to 82% pain reduction) can also be achieved in patients with chronic pain who were placed on sublingual buprenorphine after failed other opioid therapies.[59,60]

Bup/Nal versus *Methadone* in Pain Management

Methadone is a racemic mixture of two stereoisomers (L- and D-methadone) with L-methadone being 8 to 50 times more potent than D-methadone and pharmacologically more active.[61,62] It is a full agonist at the μ-opioid receptor and an antagonist at the glutamatergic *N*-methyl-D-aspartate receptor. The *N*-methyl-D-aspartate receptor plays an important role in neuronal excitation, memory, opioid tolerance, and OIH.[40,41] Acting as an *N*-methyl-D-aspartate receptor antagonist may be one mechanism by which methadone is effective in the treatment of neuropathic pain.[63] Methadone also inhibits reuptake of serotonin and norepinephrine, making it useful for the treatment of other pain conditions as well.[64] It has high oral and rectal absorption, high liposolubility, no known active metabolites, high potency, low cost, and longer administration intervals as compared with many μ-opioid receptor agonists.[65] Moreover, methadone has the potential to control pain that fails to respond to other opioids because of its incomplete cross-tolerance with other opioid analgesics.[65]

However, methadone has a number of adverse pharmacological properties. It has a long and unpredictable half-life (13 to 58 h) although, after oral administration, it can be detected in the plasma in 30 min. It has a bioavailability of approximately 80%, ranging from 41 to 95%, such that individual serum levels can vary greatly.[61,66] Methadone also interacts frequently with other medications and has significant systemic toxicity to the heart (*e.g.*, prolonged QTc

Table 3. Clinical Data on Buprenorphine in Patients with Pain without Opioid Dependence

Reference	Drug Dose and Study Duration	Type of Study	Clinical Condition	Concurrent Treatment	Clinical Outcome	Comments
Mercadante *et al.*[55] 2009	Transdermal buprenorphine at 17.5 μg/h for 4 wk	Nonrandomized, open-label, uncontrolled, observational study (n = 40)	Moderate or advanced cancer (gastrointestinal, breast, lung, and genitourinary)	Adjuvant symptomatic drugs were used as needed by physicians	The mean pain score was significantly decreased and improvement in quality of life was measured after 4 wk	*Strength:* Transdermal buprenorphine patch dose was changed every 3 d according to pain relief and the time to dose stabilization was calculated *Limitations:* A small number of subjects (24) completed the study
Breivika *et al.*[54] 2010	Transdermal buprenorphine that started at 5 μg/h and titrated up to 10 or 20 μg/h as needed for 6 mo	Randomized, double-blind, placebo-controlled clinical trial (n = 199) comparing buprenorphine with placebo	Osteoarthritis of the hip and/or knee for at least 1 yr and have radiographic evidence	Patient who took NSAIDs and COXIB were allowed to continue using them. Paracetamol 0.5–4 g was used as a rescue	24-h osteoarthritis index of pain was not significantly superior to that of placebo after 6 mo	*Strength:* 17 centers across Europe for data collection *Limitation:* Data were collected by 19 different investigators that might have led to biases in the study
Steiner *et al.*[51] 2011	Transdermal buprenorphine at 10 or 20 μg/h for 12 wk	Randomized, double-blind, placebo-controlled study (n = 1,024) comparing transdermal buprenorphine with transdermal placebo	Subjects were 18 yr or older with moderate to severe low back pain persisting for a minimum of 3 mo before study entry	Oxycodone, acetaminophen, and ibuprofen were used as rescue	The mean "average pain during the last 24-h" score was lower in patients receiving buprenorphine than placebo at week 12	*Strength:* The study had a "run-in" phase where patients were on transdermal buprenorphine for 3 d to assess which dose group they would belong to in a double-blind phase of the study *Limitations:* A large number of subjects discontinued the therapy (483 of 1,024)
Mitra *et al.*[52] 2013	Transdermal buprenorphine was started at 5 μg/h and titrated up individually for 12 mo	Randomized, open-label longitudinal study (n = 46) comparing the effectiveness of transdermal buprenorphine with transdermal fentanyl patches	Opioid-naive adult subjects with nonmalignant persistent (predominantly lower back) pain	Subjects were allowed to take over the counter medications (paracetamol) and NSAIDs as rescue medications	In total, 41% of patients on transdermal buprenorphine discontinued the treatment. Approximately 11% of patients reported sufficient pain relief after 6 mo	*Strength:* Used seven different variables to assess the treatment effectiveness and these seven variables were assessed up to 28 times a month *Limitations:* There was no placebo group to compare the effectiveness of transdermal buprenorphine. A total of 41% of subjects on the buprenorphine regimen had stopped the treatment
Yarlas *et al.*[53] 2013	Transdermal buprenorphine at 10 μg/h and 20 μg/h for 12 wk	Randomized, double-blind, placebo-controlled study (n = 1,080) evaluating the impact of transdermal buprenorphine on health-related quality of life	Moderate to severe chronic low back pain	None	Transdermal buprenorphine led to greater improvement than placebo in all aspects of health-related quality of life in the study	*Strength:* A large number of subjects *Limitations:* The study used an enrolled design that ensured the selection of subjects who were the ones receiving the treatment. This may underestimate the placebo effect

COXIB = Cox-2 inhibitor; NSAIDs = nonsteroidal antiinflammatory drugs.

Table 4. Clinical Data on Buprenorphine in Patients with Pain with Opioid Dependence

Reference	Drug Dose and Study Duration	Type of Study	Clinical Condition	Concurrent Treatment	Clinical Outcome	Comments
Böhme *et al.*[57] 2002	Transdermal buprenorphine (35, 52.5, and 70.0 μg/h; 0.8, 1.2, and 1.6 mg daily) for 5–9 d	Randomized, double-blind, clinical trial (n = 445) comparing transdermal buprenorphine in varying doses with placebo	Chronic malignant, nonmalignant (musculoskeletal, postlaminectomy, degenerative spinal pain), and neuropathic pain	None	More than 50% had good or complete pain relief; had better sleep with fewer disturbances from pain. There was an overall improvement in the quality of life	*Strength:* A dose–response design and a broad range of pain conditions *Limitation:* Unclear with regard to rescue medications
Sittl *et al.*[56] 2003	Transdermal buprenorphine (35, 52.5, and 70.0 μg/h; 0.8, 1.2, and 1.6 mg daily) for 15 d	Randomized, double-blind, placebo-controlled clinical trial (n = 157) comparing transdermal buprenorphine in varying doses with placebo	Cancer-related pain, disorder with locomotion, or neuropathic pain	Sublingual buprenorphine tablets were used for rescue. Some patients with cancer continued with chemotherapy	43.5% of subject had reduced pain, 44.5% of subjects had increased duration of sleep, and there was a 56.7% reduction in opioid use	*Strength:* Used a diary (pain, sleep pattern) to improve data collection *Limitation:* Chemotherapy was an unaccounted confounding factor
Griessinger *et al.*[58] 2005	Transdermal buprenorphine (35, 52.5, and 70.0 μg/h; 0.8, 1.2, and 1.6 mg daily) for 9 mo	Open-label, observational study (n = 13,179) comparing varying doses of buprenorphine	Cancer-related pain, musculoskeletal disorders, and neuropathic pain	13% of patients were using NSAIDs	80% of subjects reported good pain relief near day 63; 70% continued with the treatment after the study	*Strength:* A large study cohort *Limitation:* Unclear as to the standard across study centers
Malinoff *et al.*[59] 2005	Individualized dose based on previous opioid use (4–16 mg buprenorphine daily) for 2.4–16.6 mo	Nonrandomized, open-label clinical trial (n = 95)	Chronic nonmalignant pain conditions	Nicotine cessation therapy was offered to those who were nicotine dependent	86% had moderate to substantial pain relief (assessed monthly); improved mood and functioning within days or weeks	*Strength:* Individualized dosing regimen *Limitation:* No control group and no consideration of confounding factors such as emotional state, previous pain, and environmental influences
Berland *et al.*[60] 2013	Individualized dose based on previous opioid use (2–20 mg buprenorphine daily for up to 25 mo	Retrospective observational cohort study (n = 76)	Chronic back, abdominal pain, fibromyalgia	Subjects were converted from long-acting opioids to short-acting opioids; then detoxified before buprenorphine therapy	67% reported improvement in pain and functional status; an increase in employment after hospitalization	*Strength:* Individualized dosing; a cohort of patients with chronic pain (over 20 yr) *Limitation:* A complex design involving dose conversion and initial detoxification

NSAIDs = nonsteroidal antiinflammatory drugs.

intervals).[65] Methadone toxicity, particularly when used with benzodiazepines, can cause hypoxia and severe pulmonary edema, and can eventually lead to death.[67] As such, methadone could be rather difficult to manage in pain treatment and requires individualized dosing with proper monitoring for side effects.[65]

To date, it remains controversial as to whether methadone should be preferentially used, as compared with bup/nal, for opioid-dependent patients with coexisting chronic pain. A randomized, clinical trial comparing bup/nal to methadone in opioid-dependent patients with pain found that both the treatment retention rate and the analgesic effect did not significantly differ between these two drugs, but methadone was superior to bup/nal in reducing illicit opioid use.[36] In this same study, however, subjects receiving bup/nal showed better improvement in mood, energy, personality, and the psychological component of chronic pain as compared with those on methadone.[36]

Of significance to note is that bup/nal therapy is likely to be superior to methadone in at least two patient populations. In pregnant women with opioid dependence, bup/nal has been shown to be more beneficial than methadone for both opioid-dependent mothers and new born babies (fewer neonatal abstinence symptoms and higher birth weight).[68]

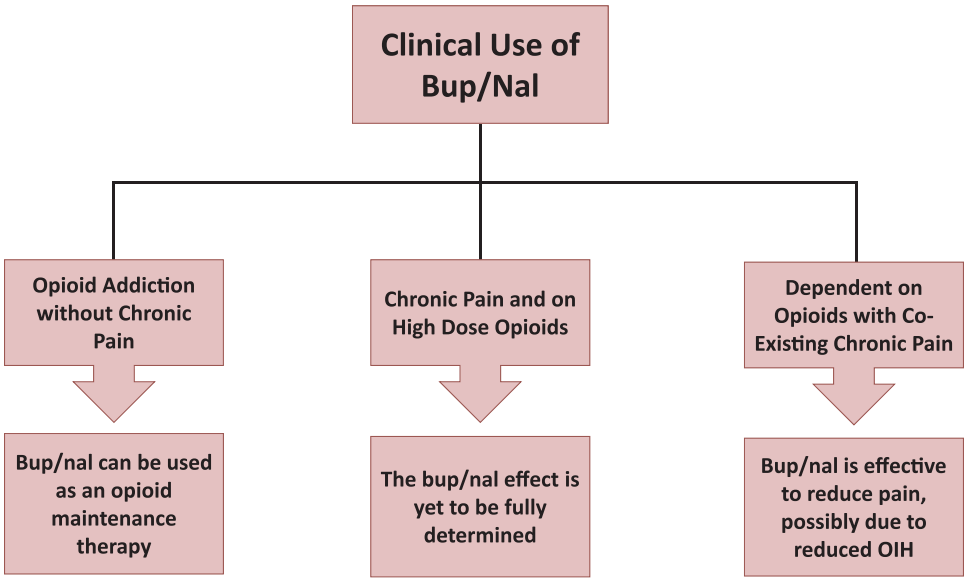

Fig. 3. A flowchart illustrating the clinical effect of buprenorphine–naloxone (bup/nal) on various categories of patients with chronic pain with or without opioid dependence or addiction. OIH = opioid-induced hyperalgesia.

Although methadone is currently the only recommended medication in the Unites States for pain management in pregnant women with opioid dependence, there has been increasing support to add bup/nal to the list. In patients with renal failure, bup/nal is also superior to methadone because the former is metabolized through the hepatic CYP3A4 system and excreted through feces.[69] Although methadone is metabolized by the hepatic CYP3A4 and CYP2B6 system, it is eliminated through the kidney and feces (the enterohepatic route). When the urine pH is below 6, as much as 30% of the methadone metabolite is eliminated through the kidney.[62,66] Therefore, a longer duration of action of methadone in patients with renal failure may lead to drug accumulation and dangerous side effects.[70]

Implications of Bup/Nal in Clinical Anesthesia and Perioperative Pain Management

Implications of bup/nal therapy in clinical anesthesia and perioperative pain management remain unclear. However, several issues warrant further examination with regard to intra- and perioperative management of patients on a bup/nal maintenance therapy. First, because buprenorphine is a partial opioid agonist with a high affinity for μ-opioid receptors, it can block other opioids from activating the same receptors. As such, patients on bup/nal therapy would be expected to require a higher dose of opioid during the intra- and perioperative period.[71] Second, a standard opioid-based anesthesia plan may be insufficient in patients on bup/nal therapy and other agents would be required to produce adequate analgesia. Third, ongoing bup/nal therapy may need to be replaced with other opioids several days (3 to 7 days) before anesthesia to ensure proper intra- and postoperative pain management. Fourth, if bup/nal therapy is replaced by other opioids preoperatively, reinstatement of bup/nal therapy postoperatively should be carefully managed to maintain adequate pain relief. Fifth, it would be of interest to determine whether buprenorphine, alone or with naloxone, would induce withdrawal symptoms in patients on high-dose opioids. To date, there is limited information regarding the impact of buprenorphine on clinical anesthesia.[72] Further studies will be needed to formulate the best clinical management plan in patients on bup/nal therapy during the intra- and perioperative period.

Summary

As summarized in figure 3, the current data suggest that bup/nal can be used as an effective outpatient office-based treatment for opioid addiction. It can also be used, as an alternative to methadone, in opioid-replacement therapy to help opioid-dependent patients reduce opioid use. Bup/nal, as a weak analgesic, seems to be not as effective in non–opioid-dependent patients with chronic pain. However, it has been successfully used for pain relief in opioid-dependent patients with chronic pain possibly due to the reversal of OIH. Future studies should address the implications of bup/nal therapy in clinical anesthesia and perioperative pain management.

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Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Mao: MGH Center for Translational Pain Research, Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts 02114. jmao@partners.org. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

References

1. Toblin RL, Mack KA, Perveen G, Paulozzi LJ: A population-based survey of chronic pain and its treatment with prescription drugs. Pain 2011; 152:1249–55
2. Johannes CB, Le TK, Zhou X, Johnston JA, Dworkin RH: The prevalence of chronic pain in United States adults: Results of an Internet-based survey. J Pain 2010; 11:1230–9
3. Compton WM, Volkow ND: Major increases in opioid analgesic abuse in the United States: Concerns and strategies. Drug Alcohol Depend 2006; 81:103–7
4. Paulozzi LJ, Budnitz DS, Xi Y: Increasing deaths from opioid analgesics in the United States. Pharmacoepidemiol Drug Saf 2006; 15:618–27
5. Kroutil LA, Van Brunt DL, Herman-Stahl MA, Heller DC, Bray RM, Penne MA: Nonmedical use of prescription stimulants in the United States. Drug Alcohol Depend 2006; 84:135–43
6. Okie S: A flood of opioids, a rising tide of deaths. N Engl J Med 2010; 363:1981–5
7. Campbell ND, Lovell AM: The history of the development of buprenorphine as an addiction therapeutic. Ann N Y Acad Sci 2012; 1248:124–39
8. Yokell MA, Zaller ND, Green TC, Rich JD: Buprenorphine and buprenorphine/naloxone diversion, misuse, and illicit use: An international review. Curr Drug Abuse Rev 2011; 4:28–41
9. Cowan A, Lewis JW, Macfarlane IR: Agonist and antagonist properties of buprenorphine, a new antinociceptive agent. Br J Pharmacol 1977; 60:537–45
10. Tejwani GA, Rattan AK: The role of spinal opioid receptors in antinociceptive effects produced by intrathecal administration of hydromorphone and buprenorphine in the rat. Anesth Analg 2002; 94:1542–6
11. Pfeiffer A, Brantl V, Herz A, Emrich HM: Psychotomimesis mediated by kappa opiate receptors. Science 1986; 233:774–6
12. Jones HE: Practical considerations for the clinical use of buprenorphine. Sci Pract Perspect 2004; 2:4–20
13. Leander JD: Buprenorphine has potent kappa opioid receptor antagonist activity. Neuropharmacology 1987; 26:1445–7
14. Chiang CN, Hawks RL: Pharmacokinetics of the combination tablet of buprenorphine and naloxone. Drug Alcohol Depend 2003; 70(2 suppl):S39–47
15. Brown SM, Holtzman M, Kim T, Kharasch ED: Buprenorphine metabolites, buprenorphine-3-glucuronide and norbuprenorphine-3-glucuronide, are biologically active. ANESTHESIOLOGY 2011; 115:1251–60
16. Cone EJ, Gorodetzky CW, Yousefnejad D, Buchwald WF, Johnson RE: The metabolism and excretion of buprenorphine in humans. Drug Metab Dispos 1984; 12:577–81
17. Jasinski DR, Pevnick JS, Griffith JD: Human pharmacology and abuse potential of the analgesic buprenorphine: A potential agent for treating narcotic addiction. Arch Gen Psychiatry 1978; 35:501–16
18. Levine JD, Gordon NC, Fields HL: Naloxone dose dependently produces analgesia and hyperalgesia in postoperative pain. Nature 1979; 278:740–1
19. Harris DS, Jones RT, Welm S, Upton RA, Lin E, Mendelson J: Buprenorphine and naloxone co-administration in opiate-dependent patients stabilized on sublingual buprenorphine. Drug Alcohol Depend 2000; 61:85–94
20. Strain EC, Moody DE, Stoller KB, Walsh SL, Bigelow GE: Relative bioavailability of different buprenorphine formulations under chronic dosing conditions. Drug Alcohol Depend 2004; 74:37–43
21. Weinhold LL, Bigelow GE, Preston KL: Combination of naloxone with buprenorphine in humans. NIDA Res Monogr 1989; 95:485
22. Simojoki K, Vorma H, Alho H: A retrospective evaluation of patients switched from buprenorphine (Subutex) to the buprenorphine/naloxone combination (Suboxone). Subst Abuse Treat Prev Policy 2008; 3:16
23. Alho H, Sinclair D, Vuori E, Holopainen A: Abuse liability of buprenorphine-naloxone tablets in untreated IV drug users. Drug Alcohol Depend 2007; 88:75–8
24. Daulouède JP, Caer Y, Galland P, Villeger P, Brunelle E, Bachellier J, Piquet JM, Harbonnier J, Leglise Y, Courty P: Preference for buprenorphine/naloxone and buprenorphine among patients receiving buprenorphine maintenance therapy in France: A prospective, multicenter study. J Subst Abuse Treat 2010; 38:83–9
25. Judd LL: Effective medical treatment of opiate addiction. National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction. JAMA 1998; 280:1936–43
26. Mintzer IL, Eisenberg M, Terra M, MacVane C, Himmelstein DU, Woolhandler S: Treating opioid addiction with buprenorphine-naloxone in community-based primary care settings. Ann Fam Med 2007; 5:146–50
27. Schackman BR, Leff JA, Polsky D, Moore BA, Fiellin DA: Cost-effectiveness of long-term outpatient buprenorphine-naloxone treatment for opioid dependence in primary care. J Gen Intern Med 2012; 27:669–76
28. Barry DT, Moore BA, Pantalon MV, Chawarski MC, Sullivan LE, O'Connor PG, Schottenfeld RS, Fiellin DA: Patient satisfaction with primary care office-based buprenorphine/naloxone treatment. J Gen Intern Med 2007; 22:242–5
29. Fiellin DA, Moore BA, Sullivan LE, Becker WC, Pantalon MV, Chawarski MC, Barry DT, O'Connor PG, Schottenfeld RS: Long-term treatment with buprenorphine/naloxone in primary care: Results at 2–5 years. Am J Addict 2008; 17:116–20
30. Parran TV, Adelman CA, Merkin B, Pagano ME, Defranco R, Ionescu RA, Mace AG: Long-term outcomes of office-based buprenorphine/naloxone maintenance therapy. Drug Alcohol Depend 2010; 106:56–60
31. Collins GB, McAllister MS: Buprenorphine maintenance: A new treatment for opioid dependence. Cleve Clin J Med 2007; 74:514–20
32. Fudala PJ, Bridge TP, Herbert S, Williford WO, Chiang CN, Jones K, Collins J, Raisch D, Casadonte P, Goldsmith RJ, Ling W, Malkerneker U, McNicholas L, Renner J, Stine S, Tusel D; Buprenorphine/Naloxone Collaborative Study Group: Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. N Engl J Med 2003; 349:949–58
33. Kamien JB, Branstetter SA, Amass L: Buprenorphine-naloxone *versus* methadone maintenance therapy: A randomised double-blind trial with opioid-dependent patients. Heroin Addict & Rel Clinical Problems 2008; 10:5–18
34. Raisch DW, Fye CL, Boardman KD, Sather MR: Opioid dependence treatment, including buprenorphine/naloxone. Ann Pharmacother 2002; 36:312–21
35. Rapeli P, Fabritius C, Alho H, Salaspuro M, Wahlbeck K, Kalska H: Methadone *vs.* buprenorphine/naloxone during early opioid substitution treatment: A naturalistic comparison of cognitive performance relative to healthy controls. BMC Clin Pharmacol 2007; 7:5
36. Neumann AM, Blondell RD, Jaanimägi U, Giambrone AK, Homish GG, Lozano JR, Kowalik U, Azadfard M: A preliminary

study comparing methadone and buprenorphine in patients with chronic pain and coexistent opioid addiction. J Addict Dis 2013; 32:68–78

37. Kreek MJ, LaForge KS, Butelman E: Pharmacotherapy of addictions. Nat Rev Drug Discov 2002; 1:710–26
38. Rosenblum A, Marsch LA, Joseph H, Portenoy RK: Opioids and the treatment of chronic pain: Controversies, current status, and future directions. Exp Clin Psychopharmacol 2008; 16:405–16
39. Rosen K, Gutierrez A, Haller D, Potter JS: Sublingual buprenorphine for chronic pain: A survey of clinician prescribing practices. Clin J Pain 2013 [Epub ahead of print]
40. Mao J: Opioid-induced abnormal pain sensitivity: Implications in clinical opioid therapy. Pain 2002; 100:213–7
41. Angst MS, Clark JD: Opioid-induced hyperalgesia: A qualitative systematic review. ANESTHESIOLOGY 2006; 104:570–87
42. Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE: Clinical pharmacology of buprenorphine: Ceiling effects at high doses. Clin Pharmacol Ther 1994; 55:569–80
43. Daitch J, Frey ME, Silver D, Mitnick C, Daitch D, Pergolizzi J Jr: Conversion of chronic pain patients from full-opioid agonists to sublingual buprenorphine. Pain Physician 2012; 15(3 suppl):ES59–66
44. Pade PA, Cardon KE, Hoffman RM, Geppert CM: Prescription opioid abuse, chronic pain, and primary care: A Co-occurring Disorders Clinic in the chronic disease model. J Subst Abuse Treat 2012; 43:446–50
45. Roux P, Sullivan MA, Cohen J, Fugon L, Jones JD, Vosburg SK, Cooper ZD, Manubay JM, Mogali S, Comer SD: Buprenorphine/naloxone as a promising therapeutic option for opioid abusing patients with chronic pain: Reduction of pain, opioid withdrawal symptoms, and abuse liability of oral oxycodone. Pain 2013; 154:1442–8
46. Kamei J, Saitoh A, Suzuki T, Misawa M, Nagase H, Kasuya Y: Buprenorphine exerts its antinociceptive activity *via* mu 1-opioid receptors. Life Sci 1995; 56:PL285–90
47. Koppert W, Ihmsen H, Körber N, Wehrfritz A, Sittl R, Schmelz M, Schüttler J: Different profiles of buprenorphine-induced analgesia and antihyperalgesia in a human pain model. Pain 2005; 118:15–22
48. Lutfy K, Eitan S, Bryant CD, Yang YC, Saliminejad N, Walwyn W, Kieffer BL, Takeshima H, Carroll FI, Maidment NT, Evans CJ: Buprenorphine-induced antinociception is mediated by mu-opioid receptors and compromised by concomitant activation of opioid receptor-like receptors. J Neurosci 2003; 23:10331–7
49. Gardell LR, Wang R, Burgess SE, Ossipov MH, Vanderah TW, Malan TP Jr, Lai J, Porreca F: Sustained morphine exposure induces a spinal dynorphin-dependent enhancement of excitatory transmitter release from primary afferent fibers. J Neurosci 2002; 22:6747–55
50. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L: A comprehensive review of opioid-induced hyperalgesia. Pain Physician 2011; 14:145–61
51. Steiner DJ, Sitar S, Wen W, Sawyerr G, Munera C, Ripa SR, Landau C: Efficacy and safety of the seven-day buprenorphine transdermal system in opioid-naïve patients with moderate to severe chronic low back pain: An enriched, randomized, double-blind, placebo-controlled study. J Pain Symptom Manage 2011; 42:903–17
52. Mitra F, Chowdhury S, Shelley M, Williams G: A feasibility study of transdermal buprenorphine *versus* transdermal fentanyl in the long-term management of persistent non-cancer pain. Pain Med 2013; 14:75–83
53. Yarlas A, Miller K, Wen W, Dain B, Lynch SY, Pergolizzi JV, Raffa RB, Ripa SR: A randomized, placebo-controlled study of the impact of the 7-day buprenorphine transdermal system on health-related quality of life in opioid-naïve patients with moderate-to-severe chronic low back pain. J Pain 2013; 14:14–23
54. Breivika H, Ljosaaa TM, Stengaard-Pedersenb K, Perssonc J, Arod H, Villumsene J, Tvinnemose D: A 6-months, randomised, placebo-controlled evaluation of efficacy and tolerability of a low-dose 7-day buprenorphine transdermal patch in osteoarthritis patients naïve to potent opioids. Scandinavian J Pain 2010; 1:122–41
55. Mercadante S, Porzio G, Ferrera P, Aielli F, Verna L, Tirelli W, Villari P, Casuccio A: Low doses of transdermal buprenorphine in opioid-naive patients with cancer pain: A 4-week, nonrandomized, open-label, uncontrolled observational study. Clin Ther 2009; 31:2134–8
56. Sittl R, Griessinger N, Likar R: Analgesic efficacy and tolerability of transdermal buprenorphine in patients with inadequately controlled chronic pain related to cancer and other disorders: A multicenter, randomized, double-blind, placebo-controlled trial. Clin Ther 2003; 25:150–68
57. Böhme K: Buprenorphine in a transdermal therapeutic system—A new option. Clin Rheumatol 2002; 21(suppl 1):S13–6
58. Griessinger N, Sittl R, Likar R: Transdermal buprenorphine in clinical practice—A post-marketing surveillance study in 13,179 patients. Curr Med Res Opin 2005; 21:1147–56
59. Malinoff HL, Barkin RL, Wilson G: Sublingual buprenorphine is effective in the treatment of chronic pain syndrome. Am J Ther 2005; 12:379–84
60. Berland DW, Malinoff HL, Weiner MA, Przybylski R: When opioids fail in chronic pain management: The role for buprenorphine and hospitalization. Am J Ther 2013; 20:316–21
61. Ferrari A, Coccia CP, Bertolini A, Sternieri E: Methadone—Metabolism, pharmacokinetics and interactions. Pharmacol Res 2004; 50:551–9
62. Chhabra S, Bull J: Methadone. Am J Hosp Palliat Care 2008; 25:146–50
63. Sotgiu ML, Valente M, Storchi R, Caramenti G, Biella GE: Cooperative N-methyl-D-aspartate (NMDA) receptor antagonism and mu-opioid receptor agonism mediate the methadone inhibition of the spinal neuron pain-related hyperactivity in a rat model of neuropathic pain. Pharmacol Res 2009; 60:284–90
64. Davis MP, Walsh D: Methadone for relief of cancer pain: A review of pharmacokinetics, pharmacodynamics, drug interactions and protocols of administration. Support Care Cancer 2001; 9:73–83
65. Ripamonti C, Zecca E, Bruera E: An update on the clinical use of methadone for cancer pain. Pain 1997; 70:109–15
66. Inturrisi CE, Colburn WA, Kaiko RF, Houde RW, Foley KM: Pharmacokinetics and pharmacodynamics of methadone in patients with chronic pain. Clin Pharmacol Ther 1987; 41:392–401
67. Caplehorn JR, Drummer OH: Fatal methadone toxicity: Signs and circumstances, and the role of benzodiazepines. Aust N Z J Public Health 2002; 26:358–62; discussion 362–3
68. Boyer EW, McCance-Katz EF, Marcus S: Methadone and buprenorphine toxicity in children. Am J Addict 2010; 19:89–95
69. Davis MP: Twelve reasons for considering buprenorphine as a frontline analgesic in the management of pain. J Support Oncol 2012; 10:209–19
70. Darke S, Duflou J, Torok M: The comparative toxicology and major organ pathology of fatal methadone and heroin toxicity cases. Drug Alcohol Depend 2010; 106:1–6
71. Bryson EO, Lipson S, Gevirtz C: Anesthesia for patients on buprenorphine. Anesthesiol Clin 2010; 28:611–7
72. Roberts DM, Meyer-Witting M: High-dose buprenorphine: Perioperative precautions and management strategies. Anaesth Intensive Care 2005; 33:17–25