A Critical Examination of the Mechanism of Action of Buprenorphine: Not Just a Mu Partial Agonist?

Leana J. Pande[1*], Stephanie D. Nichols[2], and Brian J. Piper[1,3]
[1]Geisinger Commonwealth School of Medicine, Scranton, PA 18509
[2]University of New England, Biddeford, ME 04005
[3]Center for Pharmacy Innovation and Outcomes, Geisinger Precision Health Center, Forty-Fort, PA 18704
*Master of Biomedical Sciences Program
Correspondence: lpande@som.geisinger.edu

Abstract

Buprenorphine, an analogue of thebaine, is a Schedule III opioid used for opioid-use disorder and as an analgesic. Buprenorphine is generally described as a partial mu-opioid receptor agonist with limited activity and a decreased response at the mu-receptor relative to full agonists. The mu-opioid receptor remains important clinically in defining efficacy in analgesic potential. In patients who are opioid naïve, the drug's efficacy as an analgesic is found to be equivalent to a full mu-opioid receptor agonist, despite decreased receptor occupancy and the "ceiling effect" produced from larger doses of buprenorphine. Buprenorphine's respiratory depressant effects, while less than many other opioids, are increased by benzodiazepines or alcohol. There have also been 11,000 reports involving buprenorphine and minors (age <19) to U.S. poison control centers, the preponderance (89.2%) with children. Contemporary research shows the traditionally taught pharmacology of buprenorphine does not take into account changes to receptor theory, pharmacological terminology, as well as consideration for the drug's route of administration and biologically active major metabolites.

Methods

We reviewed articles through GoogleScholar, PubMed, and Ovid databases to find relevant information regarding buprenorphine, buprenorphine's binding capability, buprenorphine's metabolites, respiratory depression, and analgesic properties. General concepts were also reviewed on UptoDate and GoogleScholar to establish definitions for receptor theory, agonists, and antagonists. We read articles that characterized buprenorphine as early as the 1970s and 1980s, all the way up to papers published in 2020. The searches were done from August 2019 through May 2020 using terms including "buprenorphine," "norbuprenorphine," "buprenorphine-3-glucuronide," or norbuprenorphine-3-glucuronide" in combination with the terms/ phrases "pharmacokinetics," "pharmacology," "receptor theory," "receptor activity," "efficacy," "respiratory depression," "ceiling effect", "analgesia," "antinociception," "pain," "metabolite," and/ or "partial agonist."

Introduction

Buprenorphine is a derivative of thebaine, which can be found in the poppy of *Papaver somniferum*. During the mid to late 1900s, buprenorphine was considered a part of the solution to what was known as the "opium problem" (1). In the 1920s, the Committee on Drug Addiction (CDA) primarily focused on morphine. At the time, the CDA looked at its multitude of uses, without its addictive side effects (1). Over 40 years later, buprenorphine was discovered in 1966, and in 1972 its agonist-antagonist pharmacological character was presented by John Lewis to the College on Problems of Drug Dependence (1), and thought to be a potential addiction treatment, first recognized in 1979 by Don Jasinski (2). Although marketed for analgesia and addiction treatment, most studies at the time found this was the "most reinforcing drug they had ever used" (1). By 1985, it was available in 29 countries (1). Buprenorphine was originally considered a Schedule V narcotic, until 2002 when it was rescheduled to Schedule III, after the Drug Enforcement Agency made three attempts to reschedule it (1). Buprenorphine is employed, with or without naloxone, for the treatment of opioid use disorder. From 2008-2019, buprenorphine distribution increased seven-fold (476.8 to 3179.9 kg) and five-fold (18.6 to 97.6 kg) to pharmacies and hospitals, respectively (3). The U.S. Medicaid program spent $1 billion on buprenorphine in 2017 alone (3).

Buprenorphine has activity at the mu, delta, and kappa, as well as the opioid receptor-like (ORL-1) also known as nociceptin, opioid receptors. There are four main opioid receptors, mu (MOR), delta (DOR), and kappa (KOR), identified in the 1960s, and the opioid receptor-like (ORL) or nociceptin (NOP), discovered in the 1990s (4). The NOP is considered an atypical, low-affinity receptor for opioid peptides (4). The mu-opioid receptor is primarily responsible for analgesic effects as well as euphoria, miosis, constipation, and respiratory depression (8). It may have a greater impact at spinal MOR relative to the brain receptors (5). Delta receptors have minimal antinociceptive effects relative to the MOR, but have more activity in chronic pain than acute pain. The DOR also participates in analgesic tolerance and physical dependence (8). The KOR has been seen to have analgesic and proalgesic effects to opioids, while also contributing to miosis and sedation (8). Buprenorphine's active metabolite, norbuprenorphine, is a potent and major metabolite that attenuates the typical analgesic effects of buprenorphine due to binding of the ORL-1 receptor. The NOP is also responsible for the respiratory depressant effects.

Buprenorphine is a unique opioid as a result of its receptor activity at the MOR (5). Buprenorphine dissociates from the mu-opioid receptor slowly, resulting in a slow duration of action (2). While most opioids show activity at the mu, delta, and kappa receptors, buprenorphine is an antagonist for the delta and kappa opioid receptors, with high affinity (6). Buprenorphine is potent at MOR and DOR, with efficacy at MOR, DOR, and the KOR, in order of descending efficacy (7).

Discussion

Buprenorphine and receptor theory

All opioids have activity at the mu receptor (9). Opioids have previously been classified as "weak" or "strong" based on their affinity for the receptor. "Weak" opioids are considered less likely to lead to addiction and adverse effects, such as respiratory depression, "Strong" opioids have greater analgesic effect and greater risk for addiction (8). Buprenorphine has antinociceptive effects that are considered primarily the result of activity at MOR (10). Traditionally, buprenorphine was described as a partial mu agonist with analgesic effects, developed to limited respiratory depression and addiction (11, 12). Since buprenorphine's initial classification, the meaning of the terms "agonist" and "antagonist" (8, 13, 14) have been more fully elucidated.

Initially, it was believed that all agonists for a receptor will result in different degrees of the same intracellular response (13,14). The transduction pathways of a drug activated by an agonist do not act identically for each receptor (4). Partial agonists are known for lack of intrinsic efficacy (16). The antinociceptive effect ascribed to buprenorphine is considered mainly mediated by mu opioid receptors (18). Bell-shaped dose-response curves of buprenorphine in the 1980s and 1990s showed there is an optimal range in concentrations for a maximum analgesic effect, with a decrease in activity below or above this range (19). The perception of buprenorphine's clinical usages may depend on the correct application or interpretation of terms from concepts in receptor theory, such as efficacy and agonist (20).

In recent years, it has become clearer that different ligands for the same receptor can cause different responses, contrary to traditional receptor theory (16). For receptor theory models to be useful, it must aid in determining the extent in which drug effects can be interpreted and applied to predict future effects (14). The term "ligand bias" has been used to describe opioid analgesic drugs which elicit a different intracellular response; therefore, their effects are not only the result of receptor binding affinity (7). Buprenorphine differentiates itself from other opioids with mu-receptor activity with its slow dissociation from the receptor (19). Buprenorphine alone is not responsible for its antagonistic effects, but its varying metabolite concentration through different forms of drug administration may alter the efficacy of the drug. The acute toxicity (LD_{50}) of buprenorphine varies based on the method of drug administration (See Table 1, from reference 21, 22). Studies have suggested that differed opioid agonists have different downstream effects in the cell, while still binding and activating the same receptor. Therefore, different opioids cannot be considered equivalent by changing the dose (8). It can no longer be assumed that any ligand activating a receptor will produce relatively the same response, with differences attributed to the agonists' efficacies (4). Ligands for a receptor can alter the downstream activity in a pathway, known as biased agonism, ligand-directed signaling, and functional selectivity (23).

Reservations regarding buprenorphine's clinical use were due to misconceptions about an analgesic "ceiling effect" (15). Data that shows a bell-shaped dose response curve displaying a ceiling effect is typically derived from animal pain models that use high doses of buprenorphine beyond what would be used clinically for humans. In humans, these curves are produced through the extrapolation of existing data (15). Until recently, agonists like buprenorphine have been known for limited intrinsic activity and inability to produce as large a response at a receptor (11, 16). Distinctions between "weak" and "strong" opioids or "full" and "partial" agonists may be needed to account for "weak" opioids like buprenorphine having characteristics considered "strong" (8). Opioids that are pure agonists such as morphine or fentanyl produce stronger analgesic effects than drugs like codeine that have decreased receptor binding (17). However, factors such as affinity and efficacy, as well as variables like metabolite binding and concurrent receptor binding may alter the perceived effects and receptor activity of buprenorphine.

Buprenorphine metabolites: receptor activity and effects

Buprenorphine's metabolism supports its analgesic effects (5). The hepatic cytochrome P (CYP) 450 (CYP P450-3A4) system metabolizes buprenorphine to norbuprenorphine through N-dealkylation of the cyclopropylmethyl group (5, 24, 25). This step allows for blood-brain barrier transport of the drug (5). Additional active metabolites are produced through the formation of conjugates with glucuronic acid with UDP glucuronosyl transferase, to produce buprenorphine-3-glucuronide and norbuprenorphine-3-glucuronide, from buprenorphine and norbuprenorphine, respectively. (5, 24, 26). Norbuprenorphine-3-glucuronide has a sedative effect and norbuprenorphine-3-glucuronide is an analgesic with low-potency (See Table 2 for a summary of buprenorphine's metabolite effects) (5).

Glucuronide metabolites of buprenorphine are biologically active, and have heterogenous binding affinity at opioid receptors. Binding affinity, the ability a drug has to bind to a receptor, is measured by the equilibrium inhibitory constant (Ki) (5). Buprenorphine has a high binding affinity at the MOR and KOR, with debatable effects (5). Studies show that the KOR receptor activity might be characterized as partial agonist (28, 70), antagonist (71), and is even thought to have no activity (21, 71). Buprenorphine-3-glucuronide had high affinity for MOR (Ki = 4.9 ± 2.7 μM), and NOR (Ki = 36 ± 0.3 μM), receptors. Norbuprenorphine-3-glucoronide had an affinity for NOR (Ki = 18 ± 0.2 μM), but not

Species	Route of Administration	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

Table 1. LD50 (acute toxicity) of buprenorphine based on the method of administration

Metabolite/ Substance	Effect	Description	Reference	Classification
BUP	Protect against respiratory depression		(30)	antagonist versus a full agonist
	Potent analgesic	Similar efficacy to NBUP	(27)	agonist
NBUP	Causes respiratory depression, potential for respiratory toxicity	A single IV dose of 3 mg kg^{-1} and 9 mg kg^{-1} induced respiratory depression	(30)	agonist
		10x greater depressant effect than BUP	(8)	
		Significant respiratory depression with 3mg kg^{-1}	(9)	
	Reduced respiratory rate		(27)	agonist
	Potent analgesic	Similar efficacy to BUP	(32,33)	agonist
	Sedation		(27)	agonist
B3G	Analgesia	¼ magnitude of BUP	(27)	unknown
N3G	Decreased tidal volume		(27)	unknown
	Sedation		(27)	unknown
	KOR mediated analgesia		(27)	unknown

Table 2. Summary of the effects of buprenorphine metabolites

	MOR	DOR	KOR	NOR
BUP	2.7 ± 0.4 pM	33 ± 1.6 nM	2.1 ± 0.2 pM	25 ± 0.3 μM
NBUP	1.8 ± 0.4 pM	1.3 ± 0.2 μM	1.3 ± 0.3 pM	No binding
B3G	4.9 ± 2.7 pM	270 ± 0.4 nM	No binding	36 ± 0.3 μM
N3G	No binding	No binding	300 ± 0.5 nM	18 ± 0.2 μM

Table 3. Receptor affinity shown as apparent Ki (inhibition constant) of buprenorphine and its metabolites, as determined by Brown et al. 2011

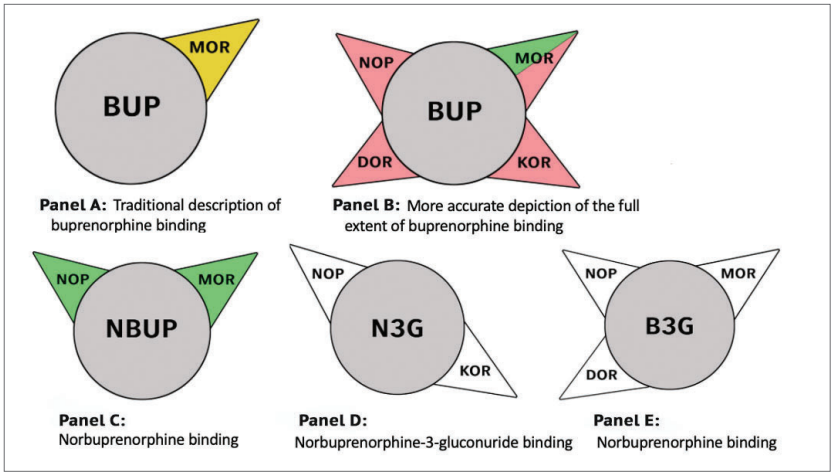

Figure 1. Visual summary of buprenorphine and buprenorphine metabolites' receptor activity

MOR (27) (See Table 3 for full list of inhibition constants and Figures 1–5 for visual summary of receptor-metabolite binding). While norbuprenorphine has a greater efficacy, it is considered a less potent partial agonist than buprenorphine at MOR (28). All metabolites except norbuprenophine-3-glucuronide have analgesic properties (27, 29).

Norbuprenorphine is the only well-researched metabolite, compared to others which need to be studied in greater detail for a greater understanding of their clinical effects. Norbuprenorphine derives from buprenorphine as a result of N-dealkylation catalyzed by cytochrome P450 in the liver (24, 25). At the MOR, both norbuprenorphine and buprenorphine are potent partial agonists, with norbuprenorphine having moderate efficacy and buprenorphine having low efficacy. At the NOP receptor, norbuprenorphine has moderate efficacy and buprenorphine having low efficacy, with both metabolites having low affinity for the receptor. This information was determined using ligand binding experiments and cAMP assay (28). In rats, the LD_{50} of buprenorphine through intravenous administration was 1,149.5 and 234.6 mg kg^{-1}, and was found to have a norbuprenorphine-to-buprenorphine LD_{50} ratio of 1/16-1/23 (30). Norbuprenorphine was 50-fold less potent than buprenorphine through intravenous administration and 4-fold less potent after intracerebroventricular (ICV) administration in in vivo animal studies. This decrease in potency may be due to poor penetration across the blood-brain barrier compared to buprenorphine (31). The intraventricular administration of buprenorphine and norbuprenorphine showed norbuprenorphine's analgesic activity was 25% that of buprenorphine (32).

Norbuprenorphine is the only well-researched metabolite, compared to others which need to be studied in greater detail for a greater understanding of their clinical effects. Norbuprenorphine derives from buprenorphine as a result of N-dealkylation catalyzed by cytochrome P450 in the liver (24, 25). At the MOR, both norbuprenorphine and buprenorphine are potent partial agonists, with norbuprenorphine having moderate efficacy and buprenorphine having low efficacy. At the NOP receptor, norbuprenorphine has moderate efficacy and buprenorphine having low efficacy, with both metabolites having low affinity for the receptor. This information was determined using ligand binding experiments and cAMP assay (28). In rats, the LD_{50} of buprenorphine through intravenous administration was 1,149.5 and 234.6 mg kg^{-1}, and was found

to have a norbuprenorphine-to-buprenorphine LD_{50} ratio of 1/16-1/23 (30). Norbuprenorphine was 50-fold less potent than buprenorphine through intravenous administration and 4-fold less potent after intracerebroventricular (ICV) administration in in vivo animal studies. This decrease in potency may be due to poor penetration across the blood brain barrier compared to buprenorphine (31). The intraventricular administration of buprenorphine and norbuprenorphine showed norbuprenorphine's analgesic activity was 25% of buprenorphine (32). While buprenorphine has a low risk for respiratory depression and is rarely considered clinically relevant in that respect, (34, 35) norbuprenorphine is a potent respiratory depressant (29). Buprenorphine's active metabolite, norbuprenorphine, was 10 times more potent than the parent drug (33). Respiratory depression can be induced by norbuprenorphine and mediated by MOR (33). Buprenorphine was found to be protective against norbuprenorphine's effect of respiratory depression, both preventing and reversing these effects. Binding experiments show DOR and, primarily, MOR as responsible for buprenorphine protecting against the norbuprenorphine-induced respiratory depression (36). Respiratory depression with the use of buprenorphine varies depending upon method of drug administration and possibly age. In a study with healthy volunteers, intramuscular buprenorphine (0.15–1.2 mg) increased the risk of respiratory depression linearly, but the effect was not clinically significant (37). With sublingual buprenorphine (1–31 mg), patients reached respiratory depression at doses 8 mg or more (38). A study on 50 postoperative patients with intravenous buprenorphine (0.4–7.0 mg) showed no signs of respiratory depression for a 24-hour period (42). Healthy volunteers with intravenous buprenorphine (0.1 mg/70 kg body weight) demonstrated a ceiling in respiratory depression, but not in analgesic efficacy (35, 39). Animal experiments show that the respiratory ceiling occurs at a lower dose (>0.2 mg/kg) than the analgesic effect ceiling, which will only occur in doses beyond the therapeutic dose range (35, 39). Experimental and clinical data show that there is a limit on buprenorphine's maximum depressant effect (15). Buprenorphine may be protective against respiratory depression, but does not account for drug interactions that can result in buprenorphine overdose or mixed route of drug administration that could increase norbuprenorphine levels. Buprenorphine reports to poison control centers, especially involving minors, are concerning. More research needs to be done to address the potential for norbuprenorphine presence to result in overdose in the presence of other drugs.

In terms of norbuprenorphine's analgesic ability, when combining results of animal and biochemical studies, norbuprenorphine and buprenorphine are considered by some to be, partial agonists at the mu receptor (31). The co-activation of the NOP receptors by buprenorphine modulates the antinociceptive effect of buprenorphine at opioid receptors (40). Additionally, the mu-opioid receptor may be responsible for counteracting the hyperalgesic effect from NOR. If mu receptors are blocked, NOR produces hyperalgesia (41). Norbuprenorphine had a high binding affinity for the mu receptor and low affinity for the NOR and presented as a potent analgesic with an efficacy equal to buprenorphine in a writhing test (28). Buprenorphine's agonistic effect at NOR is believed to counter antinociception by buprenorphine and norbuprenorphine on opioid receptors, producing the bell-shaped curves in nociceptive assays (28). Preclinical reports show NOR agonism contributes to decreased analgesia at high concentrations. However, buprenorphine's affinity for the NOR is approximately 50 times lower than its affinity for the MOR and NOR activation causing a pronociceptive effect has not been validated in clinical settings (27, 42, 43).

Analgesic effect and route of buprenorphine administration

Buprenorphine's properties including low molecular weight, high lipophilicity, and high potency (5) influence its perceived effects. Buprenorphine is 96% protein bound after absorption (5). Oral absorption is considered to be poor due to buprenorphine's "first pass metabolism" (5). Transdermal absorption is limited, Sublingual administration is considered effective Some studies consider buccal formulations to be the most efficient with the highest non-intravenous bioavailability (5).

Because of the options in different methods of drug administration (5), buprenorphine's analgesic ability does not appear to be limited and shows promise for pain treatment in patients who are opioid naïve (29, 43, 44). Preclinical studies have shown the effectiveness of buprenorphine in various pain conditions (45). In conscious rats, buprenorphine was even considered 100 times more potent than morphine (equipotent 0.03–3.0 mg/kg SC.) in paw pressure tests, but buprenorphine produced a bell-shaped dose response curve in hot plate tests. The antinociceptive effects of buprenorphine and morphine were equipotent in both paw pressure and hot plate tests when administered intrathecally at 10 micrograms (46). The paw-pressure test with subcutaneous administration showed buprenorphine was more potent than morphine (47).

The method of administration of buprenorphine has significant implications for the efficacy and benefits or detriments associated with it (29). Buprenorphine is considered a potent analgesic when administered intravenously, intramuscularly, buccally, and sublingually, from moderate to severe pain levels (44). Buprenorphine's slow onset time decreases its effectiveness for acute pain (44). However, based on the formulation and method of application, buprenorphine can be approximately 25 to 100 times more potent than morphine (2, 47, 48). Intrathecal injections of buprenorphine and morphine showed similar antinociceptive potencies after their peak, but with a shallower dose-response curve for buprenorphine. Similar results were shown through in the hot plate test, a test used for measuring acute and subcutaneous pain (46). For thermal pain, intrathecal buprenorphine was found to be 17 times more effective than hydromorphone (18). Buccal administration of buprenorphine was effective and tolerable in opioid naïve patients with moderate to severe low back pain (49, 50) and general "round-the-clock" chronic pain (51). Thirty-three clinical studies showed efficacy in buprenorphine for pain relief with 88% using transdermal buprenorphine and 12% using buprenorphine buccal film. Pergolizzi and Raffa considered buprenorphine to have the efficacy of a Schedule II buccal film and similar efficacy and tolerance to the transdermal formulation (42, 52). Buprenorphine buccal film (150–900 µg/12 h) had similar efficacy results as Schedule II hydromorphone hydrochloride (12–64 mg/12 h) (52). Sublingual buprenorphine in the tablet form was 15 times more potent than intramuscular morphine. Sublingual buprenorphine is also active longer than morphine (53) and was effective

postoperative analgesic (54–57). In postoperative cancer patients, it was found the relative potencies of intramuscular to sublingual buprenorphine is 2:1 (53). For postoperative pain by the intramuscular route, buprenorphine was found to be 30 times more potent than morphine (58–60) and have a longer duration of action than morphine in cancer patients (61).

The analgesic potency of buprenorphine (23, 47) and its lipophilicity and low molecular weight make buprenorphine ideal for transdermal delivery (15). Lower doses of transdermal buprenorphine were required to produce the same equipotency as transdermal fentanyl (47). In two case studies, buprenorphine gave a positive response where transdermal fentanyl had failed (47). Transdermal administration of buprenorphine in chronic non-cancer, neuropathic, and cancer-related pain did not antagonize analgesia and demonstrated efficacy and safety as well as reduced negative effects like withdrawal. Transdermal buprenorphine has advantages for chronic pain treatment (62–63). Compared with placebo, the initiation of transdermal buprenorphine in patients with chronic non-cancer, neuropathic, and cancer-related pain resulted in effected analgesia and showed beneficial efficacy. It was also safe, well-tolerated, and did not cause opioid withdrawal symptoms (62–63). Transdermal administration of buprenorphine was found to be efficacious and well tolerated in moderate to severe chronic low back pain (64) and long-term control of chronic pain in cancer patients (65, 45). Transdermal buprenorphine was seen to be effective for longer term chronic cancer and noncancer pain, with at least satisfactory analgesic effects reported in the preponderance (90%) of 215 patients (62). Patients with moderate to very severe chronic pain, both cancer- and non-cancer-related, slept longer uninterrupted by pain and of the 239 patients participating, 90% found satisfactory pain relief and 95% tolerated the patch well (66).

With respect to analgesia, there was no observed ceiling effect within the therapeutic dose range of buprenorphine for pain (48). Buprenorphine was a potent analgesic with full efficacy in mouse models or acute somatic and visceral pain. As a result, the analgesic efficacy of buprenorphine in those who are opioid naïve is not limited by its categorization as a partial agonist or previous reports of the bell-shaped dose response curve, with a maximal efficacy of the compound was maintained at almost 100% maximum possible effect (10). In clinical studies, no ceiling has been found with buprenorphine's analgesic effect (34, 45). In a report in humans with acute pain, ascending intravenous doses did not show any ceiling effect up to 0.6 mg of buprenorphine (roughly equivalent to 10–20 mg of intravenous morphine (39). In earlier papers classifying buprenorphine, mention of the ceiling effect seen with the MOR used dose ranges that were not relatively equivalent to the potency of other drugs it was tested against such as morphine. Morphine has been found to be 25–50 times more potent than buprenorphine as an analgesic (38, 67). A plateau was reported in the dose-effect curve of buprenorphine, however this team noted that dose comparisons between partial and full mu agonist would be made cautiously since extrapolation does not accurately estimate potency (38).

Opioids rarely bind to a single receptor and will have difference in affinities to others. Buprenorphine co-activates other receptors that may play a role in its efficacy. Some of buprenorphine's negative effects such as respiratory depression and abuse can be attributed to peripheral DOR (68). While opioid analgesics like buprenorphine often bind to the mu-opioid receptor, there is a variation in their affinity for this receptor as well as their affinity ratio for other receptors, such as the previously mentioned ORL-1 receptor, in addition to kappa and delta-opioid receptor (8). Buprenorphine has antagonistic activity at the KOR that causes antihyperalgesic effects to some extent (15). The antihyperalgesic effects of buprenorphine have successfully treated neuropathic pain (48, 62, 69), which may show neuropathic pain may be more susceptible to buprenorphine than other opioids (15). Antagonism from the KOR activation leads to predictions that drugs with lower affinity for the KOR relative to MOR will be effective in producing MOR-related effects (8). However, buprenorphine's KOR activity is controversial as this agent is characterized as a partial agonist (28, 70), antagonist (71), and even thought to have no activity (21, 71). Buprenorphine is even contested as an antagonist or inverse agonist at KOR (See Table 4 for summary of buprenorphine's analgesic efficacy) (5). Therefore, this receptor should have little role for consideration in buprenorphine's activity considering these mixed results (30). Additionally, sigma-1 receptors modulate the analgesic effects of opioids. Ablation of TRPV+ cells with high densities of sigma-1 receptors, an orphan receptor whose endogenous neuropeptide ligand is unknown, did not alter IB4+ neurons with high amounts sigma-1 receptors, mechanical nociception, or sigma-1 antagonism on morphine antinociception. It did impair response to heat stimuli and morphine's effect on heat nociception (73). Additionally, dimers of the receptors can arise as homo- or hetero-conformations, that may have distinct signals (74). MOR-DOR and DOR-KOR specific agonists have different signal, outcomes, and antinociceptive results (8, 75, 76).

Receptor Type	Effect	Reference	Classification
Mu-Opioid Receptor	Primary analgesic effect	(40,18,28)	Agonist
Kappa-Opioid Receptor	Nociceptive effect or Antinociceptive effect from spinal KOR	(27,18, 30)	Agonist or antagonist, effect debated
Nociceptin-Opioid Receptor	Attenuate MOR activity	(28)	Antagonist
	Hyperalgesic effect without MOR	(40, 28, 41)	Inverse agonist

Table 4. Summary of receptor activity associated with buprenorphine's analgesic efficacy

Discussion

The classification as a partial agonist comes in part from the reduced efficacy in morphine and other mu-opioid receptor agonists analgesics when first exposed to buprenorphine. The "antagonist profile" was a conclusion drawn from reduced efficacy if buprenorphine was injected before morphine. Buprenorphine is still a more potent analgesic than morphine and pentazocine in rat tail pressure tests, and marginally more potent than morphine in mouse and rat tail flick tests (66). Buprenorphine's pharmacology allows for it to be combined with other mu-opioid receptor agonists for an additive analgesic effect, but only when the full agonist is added to buprenorphine and not in the reverse order. The reverse causes a precipitation of acute withdrawal (45, 76). Administering intrathecal morphine and IV buprenorphine simultaneously alleviates pain with decreased sedation and other side effects than either drug alone (79). Additionally, switching between buprenorphine and full mu-agonists is possible without the loss of analgesic efficacy and without refractory period when switching from buprenorphine to new mu-opioid treatment (44, 16). Overall, clinical practice guidelines state the importance of patients self-reporting effective analgesics as pain is considered a personal experience that varies based on individual threshold and tolerance (21).

Partial antagonism is seen in animals with high dose ranges that are clinically irrelevant. Buprenorphine has a mu-agonistic profile of high potency and efficacy, as well as reversibility and no lag time for action, making it ideal for long-term pain treatment, if an opioid is absolutely necessary (44). In a partial agonist, the less than full effect should remain the same even with full receptor saturation (77). PET technology shows that buprenorphine can produce analgesia at less than full receptor occupancy Therefore, other receptors beyond the mu-opioid receptor may be responsible than analgesia (20). Buprenorphine has a high affinity for MOR, but occupies fewer receptors for analgesia. Buprenorphine increases mu-opioid receptor expression so that other mu agonists can interact with the receptors (44). Additionally, buprenorphine's activation at the MOR occurs at lower levels of receptor phosphorylation (5). When administering buprenorphine, receptors are available for full agonism at MOR for the treatment of acute pain (5).

The classification of a receptor depends on the ability of a drug to function in the environment it is presented in (5, 78). While different factors like temperature influence the agonist or antagonist activity perceived, it was determined that buprenorphine can be considered a full agonist in a clinical setting when used in people who are opioid naïve (78). Some in vitro assays have shown morphine to act as an antagonist, despite morphine being considered a full-agonist clinically (5). The bioavailability of certain metabolites in plasma, like norbuprenorphine, requires more research as this has implications on medications that can be co-administered with buprenorphine. Intravenous administration has a 100% bioavailability, buccal buprenorphine has 46–65% bioavailability, sublingual has a 28–51% bioavailability, and transdermal has a 15% bioavailability (5). Some studies show there is a significant amount of norbuprenorphine remaining in the plasma following buprenorphine's administration (80), contrary to others (32). Buprenorphine overdoses reported in the mid-2000s can be related to varied norbuprenorphine plasma concentrations (81, 82), which can be related to method of administration (36, 83). Buprenorphine's clearance in anesthetized patients was seen to be lower than individuals not under anesthesia, as well as in patients with reduced hepatic blood flow as a result of another administered anesthetic (57). Buprenorphine as a tablet has a bioavailability that is 50–60% that of a buprenorphine solution (84–85). Intranasal buprenorphine is 50% bioavailable in humans in a polyethylene glycol 300 and 5% dextrose vehicle, with a maximum concentration at 30 minutes. In sheep, buprenorphine's intranasal bioavailability was 70% with a polyethylene glycol 300 vehicle and 89% with a dextrose vehicle (86).

The full extent of buprenorphine's pharmacokinetics' is important clinically. Opioids were previous classified as "weak" or "strong" based on their affinity for the mu-opioid receptor. This is ineffective if used clinically, as "weak" opioids are considered less likely to lead to addiction and adverse side effects. Classifying buprenorphine as a weak opioid is harmful because the drug can cause physiologic dependence and has the potential for analgesic benefits, if an opioid is deemed necessary for treatment. Without taking into consideration of factors such as method of administration or distinguishing myth from fact, this can lead to incorrect assumptions in the efficacy of the opioid prescribed. Additionally, without taking into account the full effects of the metabolites' transduction based on method of administration, there can be side effects as a result of residual effects of buprenorphine's metabolism. Continued efforts to better understand the complex pharmacodynamics and pharmacokinetics of buprenorphine and metabolites will result in a better appreciation of the risks and benefits of this ubiquitous opioid.

References

1. Campbell ND, Lovell AM. The history of the development of buprenorphine as an addiction therapeutic. *Ann NY Acad Sci*. 2012; 1248:124-139.
2. 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(4): 501–516.
3. Pashmineh AA, Cruz-Mullane A, Podd JC, Lam WS, Kaleem SS, Lockard LB, et al. Rise and Regional Disparities in Buprenorphine Utilization in the United States. *Pharmacoepidemiology Drug Saf*. 2019; 29(6): 1-8.
4. Cox BM, Christie MJ, Devi L, Toll L, Traynor JR. Challenges for opioid receptor nomenclature: IUPHAR Review 9. *Br. J*. 2014; 172(2): 317-323.
5. Gudin J, Fudin J. A narrative pharmacological review of buprenorphine: A unique opioid for the treatment of chronic pain. 2020; *Pain Ther*. 2020; 9: 41-54.
6. Khroyan TV, Wu J, Polgar WE, Cami-Kobeci G, Fotaki N, Husbands SM, et al. BU08073 a buprenorphine analogue with partial agonist activity at mu-receptors in vitro but long-lasting opioid antagonist activity in vivo in mice. *Br J Pharmacol*. 2015;172(2): 668–80.

7. Kuo A. Magiera J, Rethwan N, Andersson A, Lam AL, Wyse B, Meutermans W, Lewis R, Smith M. in vitro profiling of opioid ligands using the cAMP formation assay and the beta-arrestin2 recruitment assay: No two ligands have the same profile. *Eur J Pharmacol*. 2020; 872:1-10.
8. Emery MA, Eitan S. Members of the same pharmacological family are not alike: Different opioids, different consequences, hope for the opioid crisis? *Prog Neuropsychopharmacol Biol Psychiatry*. 2019; 92:428–449.
9. Pathan H, Williams J. Basic opioid pharmacology: an update. *Br J Pain*. 2012;6(1):11–16.
10. Kögel B, Christoph T, Strassburger W, Friderichs E. Interaction of mu-opioid receptor agonists and antagonists with the analgesic effect of buprenorphine in mice. *Eur J Pain*. 2005; 9(5):599–611.
11. Rivera SM, Gilman AG. Access Medicine. *Goodman & Gilman's: The Pharmacological Basis of Therapeutics13e* New York: McGraw-Hill, 2015.
12. Ni Q, Xu H, Partilla JS, de Costa BR, Rice KC, Kayakiri H, et al. Opioid peptide receptor studies. 3. Interaction of opioid peptides and other drugs with four subtypes of the κ2 receptor in guinea pig brain *Synapse*. 1995; 16(6):60-64,
13. De Lean A, Stadel JM, Lefkowitz RJ. A ternary complex model explains the agonist-specific binding properties of the adenylate cyclase-coupled beta-adrenergic receptor. *J Biol Chem*. 1980; 255(15): 7108–7117.
14. Kenakin T. Principles: receptor theory in pharmacology. *Trends Pharmacol Sci*. 2004; 25(4):186–192.
15. Kress HG. Clinical update on the pharmacology, efficacy and safety of transdermal buprenorphine. *Eur J Pain*. 2009; 13(3):219–230.
16. Katzung BG. Access Medicine. Introduction: The nature of drugs & drug development & regulation. In: Katzung BG. eds. *Basic & Clinical Pharmacology* New York: McGraw-Hill Education 2018.
17. Gladson B, Myslinski M, Streifer M. Access Medicine. Principles of pharmacology and selective agents in physical medicine and rehabilitation. Mitra R. eds. *Principles of Rehabilitation Medicine* New York: McGraw-Hill Education 2018.
18. 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(6): 1542-6.
19. Dum JE, Herz A. In vivo receptor binding of the opiate partial agonist, buprenorphine, correlated with its agonistic and antagonistic actions. *Br J Pharmacol*. 1981; 74(3):627–633.
20. Ding Z, Raffa RB. Identification of an additional supraspinal component to the analgesic mechanism of action of buprenorphine. *Br J Pharmacol*. 2009; 157(5): 831–843.
21. Johnson RE, Fudala PJ, Payne R. Buprenorphine: considerations for pain management. *J Pain Symptom Manage*. 2005; 29(3):297–326.
22. Gueye PN, Borron SW, Risede P, Monier C, Buneaux F, Debray M, et al. Lack of effect of single high doses of buprenorphine on arterial blood gases in the rat. *Toxicol Sci*. 2001; 62(1):148–54.
23. Galandrin S, Oligny-Longpré G, Bouvier M. The evasive nature of drug efficacy: implications for drug discovery. *Trends Pharmacol Sci*. 2007; 28(8):423–430.
24. Iribarne C, Picart D, Dréano Y, Bail JP, Berthou F. Involvement of cytochrome P450 3A4 in N-dealkylation of buprenorphine in human liver microsomes. *Life Sci*. 1997; 60(22):1953–1964.
25. Kobayashi K, Yamamoto T, Chiba K, Tani M, Shimada N, Ishizaki T, et al. Human buprenorphine N-dealkylation is catalyzed by cytochrome P450 3A4. *Drug Metab Dispos*. 1998; 26(8):818–821.
26. Mistry M, Houston JB. Glucuronidation in vitro and in vivo. Comparison of intestinal and hepatic conjugation of morphine, naloxone, and buprenorphine. *Drug Metab Dispos*. 1987; 15(5):710–717.
27. Brown SM, Holtzman M, Kim T, Kharasch ED. Buprenorphine metabolites, buprenorphine-3-glucuronide and norbuprenorphine-3-glucuronide, are biologically active. *Anesthesiology*. 2011; 115(6):1251–1260.
28. Huang P, Kehner GB, Cowan A, Liu-Chen LY. Comparison of pharmacological activities of buprenorphine and norbuprenorphine: norbuprenorphine is a potent opioid agonist. *J Pharmacol Exp Ther*. 2001; 297(2):688–695.
29. Butler S. Buprenorphine—Clinically useful but often misunderstood. *Scan J Pain* 2013; 4(3),148-152.
30. Mégarbane B, Hreiche R, Pirnay S, Marie N, Baud FJ. Does high-dose buprenorphine cause respiratory depression?: possible mechanisms and therapeutic consequences. *Toxicol Rev* 2006; 25(2):79–85.
31. Coller JK, Christrup LL, Somogyi AA. Role of active metabolites in the use of opioids. *Eur J Clin Pharmacol*. 2009; 65(2):121–139.
32. Ohtani M, Kotaki H, Sawada Y, Iga T. Comparative analysis of buprenorphine- and norbuprenorphine-induced analgesic effects based on pharmacokinetic-pharmacodynamic modeling. *J Pharmacol Exp Ther*. 1995; 272(2):505–510.
33. Ohtani M, Kotaki H, Nishitateno K, Sawada Y, Iga T. Kinetics of respiratory depression in rats induced by buprenorphine and its metabolite, norbuprenorphine. *J Pharmacol Exp Ther*. 1997; 281(1):428–433.
34. Dahan A, Yassen A, Bijl H, Rohmberg R, E. Sarton, L. Teppema, et al. Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats. *Br J Anaesth*. 2005; 94(6):825–834.
35. Dahan A. Opioid-induced respiratory effects: new data on buprenorphine. *Palliat Med*. 2006; 20(8); 3-8.
36. Mégarbane B, Hreiche R, Pirnay S, Marie N, Baud FJ. Does high-dose buprenorphine cause respiratory depression?: possible mechanisms and therapeutic consequences. *Toxicol Rev*. 2006; 25(2):79–85.

37. Orwin JM, Orwin J, Price M. A double-blind comparison of buprenorphine and morphine in conscious subjects following administration by the intramuscular route. *Acta Anaesthesiol Belg*. 1976; 27(3):171–181.
38. Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE. Clinical pharmacology of buprenorphine: Ceiling effects at high doses. *Clin Pharmacol Ther*. 1994; 55(5):569–580. doi:10.1038/clpt.1994.71
39. Yassen A, Kan J, Olofsen E, Suidgeest E, Dahan A, Danhof M. Mechanism-based pharmacokinetic-pharmacodynamic modeling of the respiratory-depressant effect of buprenorphine and fentanyl in rats. *J Pharmacol Exp Ther*. 2006; 319(2):682–692.
40. Lutfy K, Eitan S, Bryant CD, Yang YC, Saliminejad N, Walwyn W, et al. Buprenorphine-induced antinociception is mediated by mu-opioid receptors and compromised by concomitant activation of opioid receptor-like receptors. *J Neurosci*. 2003; 23, 10331–10337.
41. Lutfy K, Hossain SM, Khaliq I, Maidment NT. Orphanin FQ/nociceptin attenuates the development of morphine tolerance in rats. *Br J Pharmacol*. [Internet]. 2009; 134(3):529–534.
42. Pergolizzi J, Böger RH, Budd K, Dahan A, Erdine S, Hans G, et al. Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). *Pain Pract*. 2008; 8(4):287–313.
43. Davis MP, Pasternak G, Behm B. Treating chronic pain: An overview of clinical studies centered on the buprenorphine option. *Drugs*. 2018; 78(12):1211–1228.
44. Christoph T, Kögel B, Schiene K, Méen M, De Vry J, Friderichs E. Broad analgesic profile of buprenorphine in rodent models of acute and chronic pain. *Eur J Pharmacol*. 2005; 507(1-3):87–98.
45. Khanna IK, Pillarisetti S. Buprenorphine - an attractive opioid with underutilized potential in treatment of chronic pain. *J Pain Res*. 2015; 8:859–870.
46. Bryant RM, Olley JE, Tyers MB. Antinociceptive actions of morphine and buprenorphine given intrathecally in the conscious rat. *Br J Pharmacol*. 1983; 78(4):659–663.
47. Sorge J, Sittl R. Transdermal buprenorphine in the treatment of chronic pain: results of a phase III, multicenter, randomized, double-blind, placebo-controlled study. *Clin Ther*. 2004; 26(11):1808–1820.
48. Sittl R, Likar R, Nautrup BP. Equipotent doses of transdermal fentanyl and transdermal buprenorphine in patients with cancer and noncancer pain: results of a retrospective cohort study. *Clin Ther*. 2005; 27(2):225–237.
49. Rauck RL, Potts J, Xiang Q, Tzanis E, Finn A. Efficacy and tolerability of buccal buprenorphine in opioid-naive patients with moderate to severe chronic low back pain. *Postgrad Med*. 2015; 128(1):1–11.
50. Gimbel J, Spierings EL, Katz N, Xiang Q, Tzanis E, Finn A. Efficacy and tolerability of buccal buprenorphine in opioid-experienced patients with moderate to severe chronic low back pain: results of a phase 3, enriched enrollment, randomized withdrawal study [published correction appears in Pain. 2017 Feb;158(2):366]. *Pain*. 2016; 157(11):2517–2526.
51. Hale M, Urdaneta V, Kirby MT, Xiang Q, Rauck R. Long-term safety and analgesic efficacy of buprenorphine buccal film in patients with moderate-to-severe chronic pain requiring around-the-clock opioids. *J Pain Res*. 2017; 10:233–240.
52. Pergolizzi JV Jr., Raffa RB. Safety and efficacy of the unique opioid buprenorphine for the treatment of chronic pain. *J Pain Res*. 2019 12:3299–3317. doi:10.2147/JPR.S231948
53. Wallenstein SL, Kaiko RF, Rogers AG, Houde RW. Crossover trials in clinical analgesic assays: Studies of buprenorphine and morphine. *Pharmacotherapy*. 1986; 6: 228-235.
54. Edge WG, Cooper GM, Morgan M. Analgesic effects of sublingual buprenorphine. *Anaesthesia*. 1979; 34(5):463–467.
55. Fry EN. Relief of pain after surgery. A comparison of sublingual buprenorphine and intramuscular papaveretum. *Anaesthesia*. 1979; 34(6):549–551.
56. Risbo A, Jøosrgensen BC, Kolby P, Pedersen J. Sublingual buprenorphine for premedication and postoperative pain relief in orthopaedic surgery. *Acta Anaesthesiol Scand*. 1985; 29(2):180-182.
57. Bullingham R, McQuay H, Moore R, Weir L, An oral buprenorphine and paracetamol combination compared with paracetamol alone: A single dose double-blind postoperative study. *Brit J Clin Pharmacol*. 1981; 12: 863-867.
58. Wang RI, Johnson RP, Robinson N, Waite E. The study of analgesics following single and repeated doses. *J Clinical Pharmacol*. 1981; 21: 121-125.
59. Tigerstedt I, Tammisto T., Double-blind, multiple-dose comparison of buprenorphine and morphine in postoperative pain. *Acta Anaesthesiol Scand.* 1981; 24: 462-468.
60. Mok MS, Lippmann M, Steen SN. Multidose/observational, comparative clinical analgetic evaluation of buprenorphine. *J Clinical Pharmacol*. 1981; 21(7): 323-329.
61. Kjaer M, Henriksen H, Knudsen EJ. Intramuskulaer buprenorfin og morfin i behandlingen af cancersmerter. En kontrolleret undersøgelse [Intramuscular buprenorphine and morphine in the treatment of cancer pain. A controlled study]. *Ugeskr Laeger.* 1982 ;144(18):1306–1309.
62. Likar R. Transdermal buprenorphine in the management of persistent pain - safety aspects. *Ther Clin Risk Manag*. 2006; 2(1):115–125.

63. Gordon A, Callaghan D, Spink D, Cloutier C, Dzongowski P, O' Mahony et al. Buprenorphine transdermal system in adults with chronic low back pain: a randomized, double-blind, placebo-controlled crossover study, followed by an open-label extension phase. *Clin Ther*. 2010; 32(5):844–860.

64. Steiner D, Munera C, Hale M, Ripa S, Landau C. Efficacy and safety of buprenorphine transdermal system (BTDS) for chronic moderate to severe low back pain: a randomized, double-blind study. *J Pain*. 2011;12(11):1163–1173.

65. Pace MC, Passavanti MB, Grella E, Mazzariello L, Maisto M, Barbarisi M, et al. Buprenorphine in long-term control of chronic pain in cancer patients. *Front Biosci. Pain.* 2007;12:1291–1299.

66. Radbruch L, Vielvoye-Kerkmeer A. Buprenorphine TDS: The clinical development rationale and results. *Int J Clin Pract Suppl Pain*. 2003; (133):15–24

67. Cowan A, Doxey JC, Harry EJ. The animal pharmacology of buprenorphine, an oripavine analgesic agent. *Br J Pharmacol. Pain.* 1977; 60(4):547–554.

68. Gaveriaux-Ruff C, Nozaki C, Nadal X, Henver CH, Weibel R, Matifas A, et al. Genetic ablation of delta opioid receptors in nociceptive sensory neurons increases chronic pain and abolishes opioid analgesia. *Pain*. 2011; 152(6):1238–1248.

69. Louis F. Transdermal buprenorphine in pain management – experiences from clinical practice: five case studies. *Int J Clin Pract*. 2006; 60 (10): 1330-1334. Available from: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1742-1241.2006.01109.x doi:10.1111/j.1742-1241.2006.01109.x

70. Zhu J, Luo LY, Li JG, Chen C, Liu-Chen LY. Activation of the cloned human kappa opioid receptor by agonists enhances [35S]GTPgammaS binding to membranes: determination of potencies and efficacies of ligands. *J Pharmacol Exp Ther Pain*. 1997; 282(2):676–684.

71. Romero DV, Partilla JS, Zheng QX, Heyliger SO, Ni Q, Rice KC, Lai J., Rothman RB. Opioid peptide receptor studies. 12. Buprenorphine is a potent and selective μ/κ antagonist in the [35S]-GTP-γ-S functional binding assay. *Synapse*. 1999; 34(2): 83-94.

72. Toll L, Berzetei-Gurske IP, Polgar WE, S R Brandt, I D Adapa, L Rodriguez, et al. Standard binding and functional assays related to medications development division testing for potential cocaine and opiate narcotic treatment medications. *NIDA Res Monogr*. 1998; 178:440–466.

73. Montilla-García Á, Tejada MÁ, Ruiz-Cantero MC, Bravo-Caparrós I, Yeste S, Zamanillo D. et al. Modulation by sigma-1 receptor of morphine analgesia and tolerance: Nociceptive pain, tactile allodynia and grip strength deficits during joint inflammation. *Front Pharmacol*. 2019; 10:136.

74. Rozenfeld R, Devi LA. Exploring a role for heteromerization in GPCR signalling specificity. *Biochem J.* 2011; 433(1):11–18.

75. Yekkirala AS, Banks ML, Lunzer MM, Negus SS, Rice KC, Portoghese PS. Clinically employed opioid analgesics produce antinociception via μ-δ opioid receptor heteromers in rhesus monkeys. *ACS Chem Neurosci*. 2012; 3(9):720–727.

76. Tröster A, Ihmsen H, Singler B, Filitz J, Koppert W. Interaction of fentanyl and buprenorphine in an experimental model of pain and central sensitization in human volunteers. *Clin J Pain*. 2012; 28(8):705–711.

77. Katzung BG, Kruidering-Hall M, Trevor AJ. Pharmacodynamics. *Katzung & Trevor's Pharmacology: Examination & Board Review*, 12e New York: McGraw Hill; 2019.

78. Greenwald MK, Johanson CE, Moody DE, Woods JH, Kilbourn MR, Koeppe et al. Effects of buprenorphine maintenance dose on mu-opioid receptor availability, plasma concentrations, and antagonist blockade in heroin-dependent volunteers. *Neuropsychopharmacology*. 2003; 28(11):2000–2009.

79. Beltrutti D, Niv D, Ben-Abraham R, Di Santo S, Weinbroum AA. Late antinociception and lower untoward effects of concomitant intrathecal morphine and intravenous buprenorphine in humans. *J Clin Anesth*. 2002; 14(6):441–446.

80. Gopal S, Tzeng TB, Cowan A. Characterization of the pharmacokinetics of buprenorphine and norbuprenorphine in rats after intravenous bolus administration of buprenorphine. *Eur J Pharm Sci*. 2002; 15(3):287–293.

81. Kintz P. A new series of 13 buprenorphine-related deaths. *Clin Biochem*. 2002; 35(7):513–516.

82. Pirnay S, Borron SW, Giudicelli CP, Tourneau J, Baud FJ, Ricordel I. A critical review of the causes of death among post-mortem toxicological investigations: analysis of 34 buprenorphine-associated and 35 methadone-associated deaths. *Addiction*. 2004; 99(8):978–988.

83. Kuhlman JJ Jr, Lalani S, Magluilo J Jr., Levine B, Darwin WD, Johnson RE, Cone EJ. Human pharmacokinetics of intravenous, sublingual, and buccal buprenorphine. *J Anal Toxicol*. 1996; 20(6):369–378.

84. Nath RP, Upton RA, Everhart ET, Cheung P, J.E., Shwonek P, Jones RT, et al. Buprenorphine pharmacokinetics: Relative bioavailability of sublingual tablet and liquid formulations. *J Clinical Pharmacol*. 2013; 39(6): 619-623.

85. Schuh KJ, Johanson CE. Pharmacokinetic comparison of the buprenorphine sublingual liquid and tablet. *Drug Alcohol Depend*. 1999;56(1):55–60.

86. Lindhardt K, Ravn C, Gizurarson S, Bechgaard E. Intranasal absorption of buprenorphine--in vivo bioavailability study in sheep. *Int J Pharm*. 2000; 205(1-2):159–163.