Received: 11 November 2021 | Revised: 19 April 2022 | Accepted: 14 May 2022

DOI: 10.1111/jvp.13073

JOURNAL OF Veterinary Pharmacology and Therapeutics WILEY

ORIGINAL ARTICLE

The history and pharmacology of buprenorphine: New advances in cats

Terrence P. Clark

Nexcyon Pharmaceuticals, Inc., Madison, Wisconsin, USA

Correspondence
Terrence P. Clark, Nexcyon Pharmaceuticals Inc., PO Box 259158, Madison, WI 53725, USA.
Email: clarktp@nexcyon.com

Funding information
The writing of this paper was funded by Elanco Animal Health and Nexcyon Pharmaceuticals, Inc.

Abstract

Opiates have a long history of medical use as effective analgesics associated with well-described side effects, including euphoria, respiratory depression, constipation, bradycardia, and histamine release, among others. The search for opiate analogs that retain effective analgesic qualities without detrimental side effects has yielded numerous compounds, including buprenorphine. Early studies of buprenorphine demonstrated analgesic effectiveness with a favorable safety profile, leading to the approval of formulations for use in humans. Since then, advances in receptor theory and molecular cloning of opioid receptors have led to a deeper understanding of buprenorphine pharmacology. More recent studies of receptor affinity and intrinsic activity have shown that buprenorphine is a μ- and κ-opioid receptor agonist, a nociceptin orphanin peptide agonist, and a δ-opioid receptor antagonist. Buprenorphine appears to have a primary spinal analgesic mechanism with complex supraspinal actions. It is considered a full agonist for pain but a partial agonist for other clinical endpoints such as respiratory depression. In feline medicine, buprenorphine is approved as low- and high-concentration injectable solutions, in addition to the most recently introduced long-acting transdermal formulation. Several investigational and compounded formulations have also been evaluated. There are contrasting differentiable features that include pharmacokinetics, onsets- and durations-of-action, routes of administration, and formulation constituents. Available buprenorphine formulations allow clinicians to select a formulation based on the anticipated duration of pain associated with various surgical procedures, and to provide interventions as needed. In light of the newly approved transdermal buprenorphine solution in cats and progress in buprenorphine pharmacology, the objective of this review is to examine the history and pharmacology of buprenorphine relative to full opioid agonists, where appropriate, integrating these insights into advances within feline medicine.

KEYWORDS
buprenorphine, cat, pharmacology, review, transdermal

1 | INTRODUCTION

Buprenorphine was originally synthesized as an alternative opioid analgesic with antinociceptive and narcotic antagonist properties without side effects and abuse potential (Cowan et al., 1971). Designated candidate M6029 (later RC6029-M), buprenorphine was first synthesized in 1966 from thebaine, a component of opium without opiate activity (Cowan, Lewis, & Macfarlane, 1977). Buprenorphine is of the oripavine class of opioids with the chemical designation N-cyclopropylmethyl-7 a-(I-S-hydroxy, 1,2,2-trimethylpropyl)-6,

14-endoethano-6, 7,8, 14-tetrahydronororipavine (Cowan, Lewis, & Macfarlane, 1977). It can be conceptually visualized by contrasting its structure to that of morphine (Yaksh & Wallace, 2018; Figure 1).

Early studies found buprenorphine to be approximately 20- to 40-fold more potent than morphine in rodent antinociceptive assays, with a ceiling effect on respiratory depression, little effect on gastrointestinal transit, a median lethal dose many 1000-fold greater than the median effective dose in mice, and a low potential for physical dependence (Cowan, Doxey, & Harry, 1977; Cowan, Lewis, & Macfarlane, 1977). Efficacy against postoperative pain in humans was later demonstrated for injectable and sublingual formulations, with relatively few morphine-like side effects. An injectable solution indicated for postoperative pain was approved for use in humans in 1977 in the United Kingdom and in 1982 in USA, along with evidence supporting its safety and effectiveness (Harcus et al., 1980). Over time, several formulations have been approved for the treatment of acute and chronic pain as well as opioid abuse in humans, including sublingual tablets, transdermal patches, buccal films, and an extended-release injectable solution (Table 1).

Following its introduction in human medicine, veterinarians were also interested in using buprenorphine. It was initially examined in dogs following orthopedic surgery where analgesia was comparable to morphine and pentazocine (Taylor & Houlton, 1984). With regard to its use in cats, buprenorphine began to appear in veterinary formularies in the 1990s (Hansen, 1994), although controlled clinical studies were lacking. Three pharmaceutical buprenorphine formulations have since been approved for use in cats (Table 2). The first, a low-concentration buprenorphine injectable solution (0.3 mg/ml), was approved for postoperative analgesia in the UK in 1995 ('Vetergesic; Ceva Animal Health '). Approval followed in several other global regulatory jurisdictions along with generic equivalents, but not in USA. A high-concentration injectable solution (1.8 mg/ml) developed to extend the analgesic duration-of-action was approved in USA in 2014 for the control of postoperative pain in cats ('Simbadol; Zoetis'; Table 2). Again in USA, a new buprenorphine formulation was recently approved for the control of postoperative pain in cats (Zorbium™; Elanco US Inc., NADA 141–547; Table 2). It is a non-aqueous transdermal buprenorphine solution (TBS) with a permeation enhancer intended for topical application that has an onset-of-action of 1–2 h and provides analgesia for 4 days.

The objectives of this review are four-fold: (1) to outline the fundamental pharmacological principles of buprenorphine in cats; (2) to highlight gaps in cat-specific buprenorphine pharmacology; (3) to update buprenorphine clinical pharmacology following earlier buprenorphine reviews (Bortolami & Love, 2015; Steagall et al., 2014); and (4) to integrate the five recent research papers that directly resulted in USA Food and Drug Administration (FDA) approval of TBS for use in cats into the knowledge base (Clark et al., 2022a, 2022b; Clark, Linton, Freise, Reinemeyer, et al., 2022; Freise et al., 2022).

2 | PHARMACOLOGY AND MECHANISM OF ACTION

2.1 | Opioid receptors

Buprenorphine was synthesized prior to the introduction of receptor theory. Modern opioid research began in 1973 with the first demonstration of opioid receptors (Pert et al., 1973; Simon et al., 1973; Terenius, 1973) through stereoselective binding assays (Goldstein et al., 1971). Brain extracts were isolated and later identified as endogenous opioids that, when applied to guinea pig ileum and mouse vas deferens, mimicked the actions of morphine (Lord et al., 1977). Binding specificity studies demonstrated multiple opioid receptors categorized by their differential selectivity for [^{3}H]enkephalins compared to [^{3}H]opiates. Morphine-preferring receptors were designated mu (μ)-opioid receptors, enkephalin-preferring receptors were designated delta (δ)-opioid receptors based upon the "d" in vas deferens assays used for characterization, while kappa (κ)-opioid receptors were named based on their selectivity for ketocyclazine (Lord et al., 1977; Martin et al., 1976).

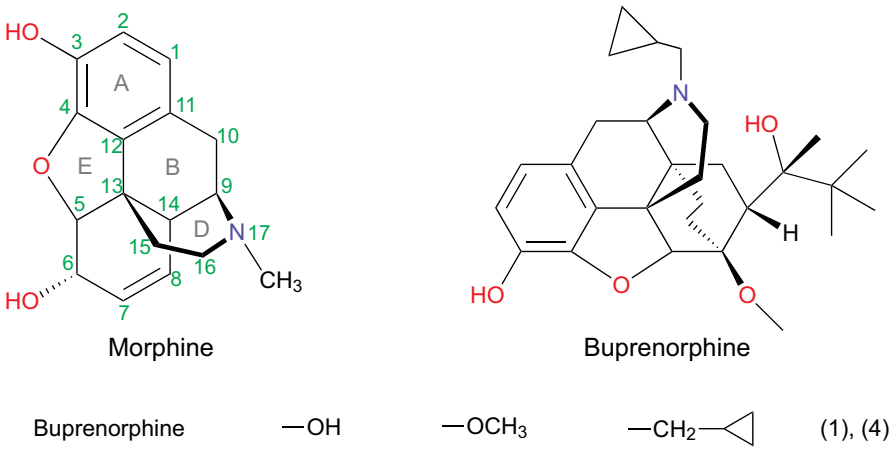


FIGURE 1 Chemical structure of morphine and the structural differences of buprenorphine. Adapted from Yaksh and Wallace (2018)

TABLE 1 Buprenorphine-containing formulations approved for use in humans

Approval date	Proprietary name	Dosage form	Route	Strength	Indication
1977	Temgesic™ (Indivior, UK)	Injectable	Injection	0.3 mg/ml	Pain
1980	Temgesic™ (Indivior, UK)	Tablet	Sublingual	2 and 8 mg	Pain
1982	Buprenex™ (Indivior, USA)	Injectable	Injection	0.3 mg/ml	Pain
2002	Subutex™ (Indivior, USA)	Tablet	Sublingual	2 and 8 mg	Pain and opioid dependence
2002	Suboxone™[a] (Indivior, USA)	Tablet	Sublingual	2 and 8 mg	Pain and opioid dependence
2002	Transtec™ (Napp, UK)	Patch	Transdermal	35, 52.5, and 70 μg/h	Pain
2010	Butrans™ (Purdue Pharma, USA)	Film, extended release	Transdermal	5, 7.5, 10, 15, and 20 μg/h	Pain
2010	Suboxone™[a] (Indivior, USA)	Film	Buccal, sublingual	2, 4, 8, and 12 mg	Pain and opioid dependence
2013	Zubsolv™[a] (Orexo, USA)	Tablet	Sublingual	0.7, 1.4, 2.9, 5.7, 8.6, and 11.4 mg	Pain and opioid dependence
2014	Bunavail™[a] (Biodelivery Sciences International Inc, USA)	Film	Buccal	2.1, 4.2, 6.3 mg	Pain and opioid dependence
2015	Belbuca™ (Biodelivery Sciences International, USA)	Film	Buccal	0.075, 0.15, 0.3, 0.45, 0.6, 0.75, and 0.9 mg	Pain and opioid dependence
2016	Probuphine™ (Titan Pharmaceuticals, USA)	Implant	Implantation	80 mg/implant	Pain and opioid dependence
2017	Sublocade™ (Indivior, USA)	Solution, extended release	Subcutaneous	100 mg/0.5 ml and 300 mg/1.5 ml	Pain and opioid dependence
2018	Cassipa™[a] (Teva, USA)	Film	Sublingual	16 mg	Opioid dependence
2018	Buvidal™ (Camurus, EU)	Solution, prolonged release	Subcutaneous injection	8, 16, 24, 32 mg	Opioid dependence
2019	Sixmo™ (Molteni Farmaceutici, EU)	Implant	Implantation	74.2 mg	Opioid dependence

[a]Contains naloxone.

2.2 | Molecular biology of receptors

Advancements in molecular biology led to breakthrough understanding of opioid receptor structure and function, elucidating buprenorphine pharmacology. The first opioid receptor to be cloned was the δ-1 (Evans et al., 1992; Kieffer et al., 1992), followed by μ-1 (Chen, Mestek, Liu, Hurley, & Yu, 1993; Eppler et al., 1993; Thompson et al., 1993; Wang et al., 1993) and κ-1 (Chen, Mestek, Liu, & Yu, 1993; Li et al., 1993; Meng et al., 1993). Each opioid receptor is encoded by a single gene termed OPRM1 (μ), (Pasternak et al., 1980; Pasternak & Snyder, 1975; Wolozin & Pasternak, 1981), OPRD1 (δ; Jiang et al., 1991), and OPRK1 (κ; Clark et al., 1989; Rothman et al., 1990; Zukin et al., 1988; Table 3). Through molecular cloning or bioinformatic analysis, the phylogeny and species variations in the μ-1 protein sequence have been characterized for over 45 species, except for cats (Pan & Pasternak, 2011; Figure 2). However, a putative sequence for the feline OPRM1 gene was recently reported ('Feline Mu-type opioid receptor 2022)' Pontius et al., 2007; Table 3). Delta- and κ-opioid receptor phylogeny has also been described in various species, except for cats (Walwyn et al., 2011; Wei & Loh, 2011).

The nociceptin orphanin peptide (NOP; opioid receptor like [ORL] or κ-3) was identified soon after the δ-opioid receptor was cloned (Bunzow et al., 1994; Chen et al., 1994; Fukuda et al., 1994; Homberg et al., 2009; Keith et al., 1994; Mollereau et al., 1994; Nishi et al., 1994; Pan et al., 1994; Pan et al., 1995; Table 3). The function of the cloned receptor was later clarified with the identification of its endogenous ligand. The latter has two names, orphanin FQ (OF/Q; Reinscheid et al., 1995) or nociceptin (N; Meunier et al., 1995), as it was independently identified by two groups. While implicated in buprenorphine's mechanism of action (see *Analgesic Mechanism* below), NOP has not yet been cloned in cats.

2.3 | Receptor affinity and intrinsic activity

The initial study to evaluate buprenorphine opioid receptor affinity in isolated tissues revealed approximately equal affinity for μ- and κ-opioid receptors as well as 10-fold lower affinity for δ-opioid receptors (Sadee et al., 1982; Villiger & Taylor, 1981). With the cloning and expression of various receptor types into functional cell systems, a more accurate comparative affinity and selectivity of buprenorphine has been reported (Olson et al., 2019). Buprenorphine has the highest binding affinity (i.e., K*i*) for μ-opioid receptors, which is 38, 30, and 477 times greater than for δ- and κ-opioid receptors, and NOP, respectively (Table 4). Moreover, buprenorphine has an 82-fold

TABLE 2 Buprenorphine-containing formulations approved for use in cats

Approval date	Proprietary name	Dosage form	Route	Strength	Indication	Dosage and administration
1995	Vetergesic™[a] (CEVA, UK and others)	Injectable	Intramuscular or intravenous injection	0.3 mg/ml	Postoperative analgesia	0.01–0.02 mg per kg body weight, repeated if necessary, once, after 2 h
2014	Simbadol™[b] (Zoetis, USA)	Injectable	Subcutaneous injection	1.8 mg/ml	For the control of postoperative pain associated with surgical procedures in cats	0.24 mg/kg 1 h prior to surgery and then once daily for up to 3 days
2022	Zorbium™ (Elanco, USA)	Transdermal	Topical	8 mg (0.4 ml), 20 mg (1 ml)	For the control of postoperative pain associated with surgical procedures in cats	8 mg (0.4 ml) to cats 1.2–3 kg and 20 mg (1 ml) to cats >3–7.5 kg. A single topical dose is applied 1–2 h prior to surgery, providing analgesia for 4 days

[a]The originally approved formulation was by Alstoe. Since its first approval, there have been additional approvals, including generic equivalents, in global regulatory jurisdictions that include single-use and multi-dose vials.
[b]The originally approved formulation was by Abbott Laboratories.

greater affinity for μ-opioid receptors compared to morphine and no affinity for cannabinoid receptor type 1, σ-1 opioid receptors, norepinephrine, serotonin, or dopamine receptors. These affinities have been confirmed in the rat and monkey brain (Table 5; Lutfy & Cowan, 2004).

The high affinity of buprenorphine for μ-opioid receptors has clinical implications. In organ preparation studies, buprenorphine exerted a gradual effect on the guinea pig ileum, peaking in about an hour, while high concentrations of naloxone failed to antagonize buprenorphine (Lewis, 1985). The rate of drug removal from the receptor, rather than the presence of the antagonist, was ultimately responsible for functional restoration. The half-life of dissociation from the μ-opioid receptor was 166 min for buprenorphine, as opposed to 7 min for fentanyl (Boas & Villiger, 1985). The tightness of binding to opioid receptors and unique receptor kinetics was suggested to have clinical implications: (1) the acute effects of buprenorphine are difficult to antagonize once bound to receptors, and (2) buprenorphine has a long duration of action. Therefore, when this high affinity is considered in a clinical context, plasma concentrations may not translate into efficacy.

Opioid receptors belong to the G-protein-coupled receptor family, the largest gene family within the mammalian genome (Fredriksson et al., 2003). Buprenorphine intrinsic activity (i.e., the magnitude of activation) in the [^{35}S]GTPγS binding assay has been examined using opioid receptor-expressing cells. Buprenorphine exhibited activity in μ-, κ-, and NOP-, but not in δ-opioid receptor expressing (i.e., is an antagonist) Chinese hamster ovary cells (Table 6). Intrinsic activity following application onto cells or tissues contrasts with measurable endpoints (or efficacy) in animals. Clinically, efficacy is a property of the drug plus the specific system and may vary based on species or endpoint assessed. A drug can act as a full agonist on one endpoint (e.g., pain) and a partial agonist on another (e.g., respiration). Thus, in a clinical setting, the term partial agonist is not a property of the drug per se and only has validity as a functional descriptor for the endpoint being examined.

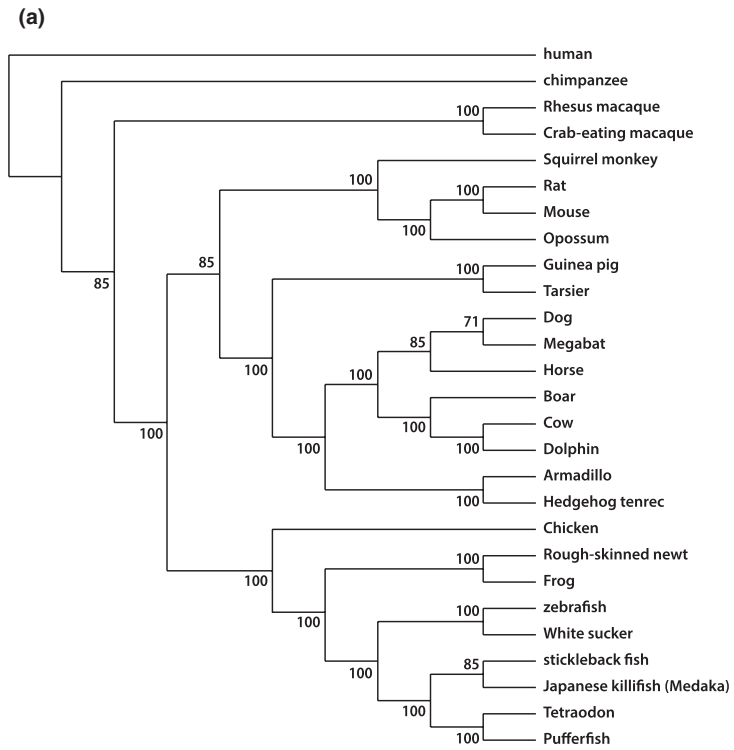
2.4 | Feline opiate system

There is a long history of laboratory and clinical studies on the characterization of pharmacological responses to opioids in cats. Morphine's effects, for example, were explored in the early 20th century (Stewart & Rogoff, 1922). A number of opioids, including buprenorphine, have been reviewed up until 2015 (Bortolami & Love, 2015; Steagall et al., 2014). However, as described above, feline opioid receptors have not yet been cloned or expressed in functional cells. The complexity of opioid receptor expression and function in other species, including splice variants, receptor dimerization, and thousands of single nucleotide polymorphisms (SNP), complicate mechanistic studies in cats (Pan et al., 2005). Moreover, cats exhibit unique responses to opioids, including mydriasis and hyperthermia, suggestive of potentially novel mechanisms (see *Ocular* and *Thermoregulation* below).

TABLE 3 Recommended opioid receptor nomenclature by the International Union of Pharmacology Receptor Nomenclature Committee (IUPHAR-NC), endogenous ligands, and the gene that codes for each receptor

IUPHAR-NC recommended name	Other names	Presumed endogenous ligand	Human gene	Rat/mouse gene	Feline gene
Mu (μ) opioid peptide receptor	MOR, OP_3	β-endorphin, Enkephalins	OPRM1	Oprm1	OPRM1[a]
Delta (δ) opioid peptide receptor	DOR, OP_1	β-endorphin, Enkephalins	OPRD1	Oprd1	Not identified
Kappa (κ) opioid peptide receptor	KOR, OP_2	Dynorphin A, Dynorphin B, α-neoendorphin	OPRK1	Oprk1	Not identified
Nociceptin orphanin peptide (NOP) receptor	ORL1, LC132, OP_4	Nociceptin/orphanin FQ	OPRL1	Oprl1	Not identified

[a]Adapted from Pontius et al. (2007); Hillier et al. (2011); 'Feline Mu-type opioid receptor'.



(b)

	Exon 4	Exon 7	Exon 11
Mammals			
Human	12aa	30aa	24aa
Chimpanzee	12aa (100%)	30aa (100%)	24aa (92%)
Rhesus macaque	12aa (100%)	30aa (100%)	32aa (72%)
Crab-eating macaque	12aa (100%)		
Squirrel monkey	12aa (100%)	30aa (80%)	
Rat	12aa (100%)	30aa (70%)	23aa (25%)
Mouse	12aa (100%)	30aa (70%)	27aa (25%)
Opossum	12aa (100%)	32aa (53%)	
Guinea pig	12aa (100%)	12aa (92%)*	24aa (67%)
Tarsier	12aa (100%)		
Dog	12aa (100%)	30aa (90%)	
Megabat	12aa (100%)	12aa (92%)*	23aa (60%)
Horse	12aa (100%)	12aa (100%)*	
Boar	12aa (100%)		
Cow	12aa (92%)	12aa (92%)*	32aa (34%)
Dolphin	12aa (92%)	12aa (100%)*	
Armadillo	12aa (92%)	109aa (83%)*	24aa (47%)
Hedgehog tenrec	12aa (75%)		
Birds			
Chicken	12aa (75%)	12aa (75%)*	

FIGURE 2 Phylogeny and species variations in the μ-1 protein sequences. (a) Phylogenetic analysis of the deduced μ-1 protein sequences. (b) Comparison of amino acid sequences predicted from exons 4, 7, 11 in mammals. Aa is number of amino acids identified; % is the percentage of homology compared to human sequences; * asterisk percentage is the comparison to the first 12 amino acids of the human sequence; from Pan and Pasternak (2011). The feline μ opioid receptor has not been described and is not included on this paradigm

As opposed to cats, rodent opioid receptor classes and subtypes have been mapped throughout the brain and spinal cord (Pasternak & Pan, 2013). Despite the lack of cloned feline opioid receptors and validated molecular probes, several studies have examined anatomic opioid receptor class distribution utilizing opioid ligands with putative specific affinity, selectivity, and intrinsic activity in cats. This includes systems involved in vision, respiration, and the spinal cord (Table 7), sites associated with buprenorphine action.

2.5 | Analgesic mechanism

Buprenorphine exerts its antinociceptive effects largely via μ-opioid receptors. Buprenorphine does not induce antinociception in μ-opioid receptor deficient CXBK mice (Kamei et al., 1997) nor in the presence of selective μ-opioid receptor antagonists (Kamei et al., 1995; Mizoguchi et al., 2003). Moreover, buprenorphine antinociception is not reduced in the presence of selective κ- or δ-opioid receptor antagonists in CXBK mice or in mice strains that express μ-, κ-, and δ-opioid receptors (Kamei et al., 1997). A further complexity is that buprenorphine analgesia depends on the expression of two μ-opioid receptor splice variants (Grinnell et al., 2016). In genetic models, disruption of δ- and κ-opioid receptors and NOP had no impact on buprenorphine analgesia, while loss of full length or truncated μ-opioid receptor splice variants eliminated buprenorphine analgesia. This effect was unique to analgesia as inhibition of gastrointestinal transit and stimulation of locomotor activity were independent of truncated μ-opioid receptor splice variants.

TABLE 4 Competition radioligand binding affinity values of buprenorphine and other opioids determined in various cell lines expressing the indicated receptor types. From Olson et al. (2019)

	Target binding affinity determined by competition radioligand binding-K_i (nM)								
Drug	**μ**	**δ**	**κ**	**NOP**	**CB1[a]**	**σ1R[b]**	**NET[c]**	**SERT[d]**	**DAT[e]**
Buprenorphine	0.90 ± 0.1	34 ± 27	27 ± 13	430 ± 100	>2000	NC	NC	NC	>2000
Hydrocodone	1800 ± 470	>2000	NC	NC	NC	4000 ± 1300	NC	NC	NC
Hydromorphone	9.4 ± 2.6	310 ± 150	1600 ± 720	NC	NC	NC	NC	NC	NC
Morphine	74 ± 18	2500 ± 720	>2000	NC	NC	NC	NC	NC	NC
O-Desmethyl-Tramadol	1300 ± 290	NC	>2000	NC	NC	NC	NC	NC	NC
Oxycodone	780 ± 170	NC	>2000	NC	NC	NC	NC	NC	NC
Oxymorphone	11 ± 1.8	>2000	>2000	NC	NC	NC	NC	NC	NC
Tapentadol	2100 ± 84	NC	>2000	NC	NC	2600 ± 410	NC	>2000	>2000
Tramadol	NC	NC	890 ± 33	NC	NC	NC	NC	>2000	>2000
Naloxone	14 ± 1.9	520 ± 110	270 ± 46						
Nociceptin				0.71 ± 0.3					

Note. The K_i values are reported as the mean ± SEM calculated from $N \geq 3$ independent experiments. NC = not converged (no binding detected). >2000 = incomplete curve without full ligand displacement at 10 μM, suggesting a $K_i > 2000$ nM.

[a]Cannabinoid receptor type 1.

[b]Sigma-1.

[c]Norepinephrine.

[d]Serotonin.

[e]Dopamine.

TABLE 5 Apparent K_i values of buprenorphine for the various members of the opioid receptor family. Data are presented as the mean ± SEM (nM). From Lutfy and Cowan (2004)

	μ	**δ**	**κ**	**NOP**
Rat brain	0.08 ± 0.02	0.42 ± 0.04	0.11 ± 0.05	285 ± 30
Monkey brain	0.08 ± 0.01	0.82 ± 0.11	0.44 ± 0.08	ND

Abbreviation: ND, not determined.

TABLE 6 EC_{50} values and maximal response of buprenorphine in stimulating [^{35}S]GTPγS binding to membranes of Chinese hamster ovary cells transfected with various members of the opioid receptor family. Data are presented as the mean ± SEM. From Lutfy and Cowan (2004))

	μ	**δ**	**κ**	**NOP**
EC50	0.08 ± 0.01 nM	NS	0.04 ± 0.01 nM	35 ± 30 nM
Percent stimulation	38 ± 8%	NS	10 ± 4%	60 ± 10%

Abbreviation: NS, no stimulation.

In addition to μ-opioid receptors, the totality of the effects of buprenorphine is the result of its concomitant binding and action on κ- and δ-opioid receptors, and NOP, which may account for the partial agonistic properties observed with some endpoints. The submaximal response in some endpoints is due to δ-mediated autoinhibition of μ- and κ-opioid receptor agonist actions (Kitzmiller et al., 2015; Lutfy & Cowan, 2004). The antinociceptive efficacy of buprenorphine is reduced by concomitant buprenorphine-mediated NOP activation, i.e., the μ-opioid receptor-mediated antinociceptive effect of buprenorphine is attenuated by its ability to activate NOP. Buprenorphine induces greater antinociception in mice lacking NOP, an effect not observed with morphine, which does not interact with NOP (Lutfy et al., 2003). In addition, the antinociceptive effect of buprenorphine is enhanced in the presence of the NOP antagonist J-113397, in wild type mice, but not in mice lacking NOP (Kawamoto et al., 1999). Thus, buprenorphine-mediated NOP agonism contributes to the ceiling effect of buprenorphine as well as attenuates the antinociceptive effects of other μ-opioid receptor agonists when co-administered (Lutfy et al., 2003). In sum, buprenorphine analgesia is complex and requires multiple μ-opioid receptor splice variants as well as κ- and δ-opioid receptors, and NOP.

Of note, buprenorphine was recently shown to harbor monoamine transporter activating properties (Olson et al., 2019). In an antinociception mouse model, the monoamine transporter inhibitor duloxetine selectively promoted buprenorphine antinociception while exerting no effects by itself or in combination with the μ-opioid receptor selective drug oxymorphone (Olson et al., 2019). The ligand–receptor interaction and downstream signaling pathways suggest additional complexity beyond that conveyed by pharmacology screening alone. Further, such novel interactions could be relevant in vivo, but the effect of duloxetine co-administration on buprenorphine-induced analgesia has not been studied in cats.

Anatomically, central nervous system regions sensitive to morphine were initially identified by administering morphine into discrete areas via microinjection in rhesus monkey brains (Pert & Yaksh, 1974). Opioids exerted their effects in the periaqueductal gray, nucleus raphe magnus, nucleus reticularis gigantocellularis, locus coeruleus, and dorsal horn. Buprenorphine appears to have a primary spinal analgesic mechanism with complex supraspinal actions. In a series of studies in mice, buprenorphine was antagonized by intraperitoneal and spinal (i.e., intrathecal) naloxone but not supraspinal (i.e., intracerebroventricular) naloxone (Ding & Raffa, 2009). In contrast, morphine and fentanyl were antagonized by intrathecal and intracerebroventricular naloxone. Buprenorphine-induced antinociception in the brain is not mediated via the usual (i.e., naloxone- and pertussis toxin-sensitive) opioid receptors or NOP, and there is a mechanistic difference between the supraspinal buprenorphine signaling and those of morphine and fentanyl.

The spinal action of buprenorphine has been examined in cats. In decerebrate cats, buprenorphine facilitated the C-fiber reflex, suggesting a lack of spinal analgesia, whereas morphine and the κ-opioid receptor agonist ethylketazocine completely suppressed the reflex (Bell & Shannon, 1988). These findings have not yet been replicated and may be unique to the decerebrate cat model. The clinical effects of epidural buprenorphine in cats supported the involvement of a spinal mechanism (Duke-Novakovski et al., 2011; Pypendop et al., 2006, 2008; Steagall et al., 2009). In a thermal threshold model, epidural morphine and buprenorphine had a duration from 1 to 16 h and 1 to 10 h, respectively (Pypendop et al., 2008). In another study, epidural buprenorphine increased thermal thresholds from 30 min to 1 h after administration and remained above the upper 95% confidence interval (CI) from 15 min to 24 h (Steagall et al., 2009). When buprenorphine plasma concentrations were measured after administering buprenorphine into the lumbosacral epidural space of cats, peak plasma concentrations were observed 15 min after injection (5.82 ± 3.75 ng/ml) and had declined by 24 h (1.40 ± 0.62 ng/ml). As these systemic concentrations are somewhat parallel to those observed following buccal buprenorphine administration, prolonged analgesia following epidural administration could be the result of spinal and systemic concentrations (Gulledge et al., 2018; Hedges, Pypendop, Shilo-Benjamini, et al., 2014; Robertson, Taylor, Bloomfield, & Sear, 2001; Stathopoulou et al., 2018; Wells et al., 2008). The contrasting effects of spinal versus supraspinal buprenorphine have not been evaluated via intracerebroventricular administration to determine feline mechanisms of analgesia.

Norbuprenorphine is the major N-dealkylated metabolite of buprenorphine initially described in rats (Brewster et al., 1981a). Norbuprenorphine was 50- to 200-fold less potent than buprenorphine with regards to its respiratory depressant or antinociceptive effects (Yassen et al., 2007). Other studies suggest a possible complex role for norbuprenorphine. In cloned receptor systems,

TABLE 7 Anatomic site distribution of opioid receptor types in the feline brain and spinal cord based on binding studies using specific ligands or antibodies

Anatomic site	Ligand or antibody	Receptor type	Reference
Superior colliculus			
Superficial layers	[Met5]enkephalin	δ, μ-1	Graybiel et al. (1984)
Deep layers	[Leu5]enkephalin	δ, μ-1	
Cortex, thalamus, and midbrain	[3H][D-Ala, N-Me-Phe, Gly(ol)] enkephalin (DAMGO)	μ	Walker et al. (1988)
	[3H][D-Pen]enkephalin (DPDPE)	δ-1	
	[3H]bremazocine	κ	
Ventrolateral medulla	[Met]enkephalin	δ, μ-1	Pokorski et al. (1981); Pokorski and Lahiri (1981); Monti-Bloch and Eyzaguirre (1985)
	[Leu]enkephalin	δ, μ-1	
Carotid body (glomus cells)	[Met]enkephalin	δ, μ-1	Kirby and McQueen (1986); Hansen et al. (1982); Wharton et al. (1980); Lundberg et al. (1979)
	[Leu]enkephalin	δ, μ-1	
	[D-Ala, D-Leu]enkephalin	δ, μ-1	
	[D-Pen, D-Pen]enkephalin (DPDPE)	δ-1	
Caudate nucleus and putamen	[Met]enkephalin	δ, μ-1	Graybiel and Chesselet (1984)
	Dynorphin B	κ	
Spinal cord	Dynorphin B	κ	Flamm et al. (1985); Faden and Jacobs (1985))
	WIN 44,441-3	κ	

norbuprenorphine has high affinities for μ-, δ-, and κ-opioid receptors, comparable to those of buprenorphine (Huang et al., 2001). In a [^{35}S]GTPγS binding assay, norbuprenorphine acted as a potent full agonist of δ-opioid receptors in contrast to buprenorphine that had no agonist activity, antagonizing norbuprenorphine (Huang et al., 2001). At NOP, norbuprenorphine was a full agonist with low potency, while buprenorphine was a potent partial agonist (Huang et al., 2001). Norbuprenorphine is also present in cats (Doodnaught et al., 2017; Taylor et al., 2016) but its overall contribution to buprenorphine analgesia appears negligible. Multiple models were evaluated to characterize the contribution of norbuprenorphine to thermal antinociception, but the PD parameters for norbuprenorphine could not be determined (Doodnaught et al., 2017).

From a clinical perspective, buprenorphine has been characterized as a partial opioid agonist, implying that it elicits a submaximal analgesic effect compared to full opioid receptor agonists. Buprenorphine produced a bell-shaped dose–response curve in the mouse tail-flick model (i.e., antinociceptive effects reach a maximum and decline at higher doses; Cowan, 2003). However, the observation that buprenorphine produces a bell-shaped dose–response curve was later shown to be unique to the rodent model used (Lewis, 1985). This concept of buprenorphine's clinical analgesic properties as a partial agonist has been revisited in reviews of basic research and clinical data (Pergolizzi et al., 2010; Raffa et al., 2014; Raffa & Ding, 2007). In the same in vitro assays of intrinsic activity, both buprenorphine and morphine produced a less than maximal effect (Traynor, 2012). In a variety of rodent models different from the tail-flick model, buprenorphine has been shown to elicit a full analgesic effect (Christoph et al., 2005) dependent upon stimulus intensity (Raffa & Ding, 2007). Still, the notion that morphine and other 'full agonists' provide greater analgesia persists. However, in a review of clinical studies in humans, buprenorphine produced equivalent or greater analgesia compared to morphine, fentanyl, sufentanil, and oxycodone (Raffa et al., 2014). A consensus group has established buprenorphine as a full agonist for the endpoint of pain (i.e., analgesia) in human patients (Pergolizzi et al., 2010).

Compared to morphine or other full agonists, the analgesic action of buprenorphine has not been explicitly examined in cats so as to conclude whether it is a full agonist for the endpoint of pain in feline clinical practice. An ideal study would compare buprenorphine with a full opioid agonist across increasing doses against moderate to severe pain without the confounding of effects of other analgesics. There have been several studies in cats undergoing surgery where a head-to-head comparison of point doses of buprenorphine and a full opioid agonist were examined. In cats undergoing ovariohysterectomy, a single intramuscular (IM) postoperative dose of buprenorphine was superior to pethidine based on the numbers of rescue analgesia interventions (Slingsby & Waterman-Pearson, 1998). In cats undergoing onychectomy, onychectomy plus castration, or onychectomy plus ovariohysterectomy, a single IM dose of buprenorphine was superior to oxymorphone in terms of the lowest cumulative pain scores and serum cortisol levels (Dobbins et al., 2002). In cats undergoing fracture repair, a five-day postoperative regimen of subcutaneous (SC) buprenorphine and levomethadone conferred comparable analgesia, although neither provided sufficient analgesia in the postoperative phase as monotherapy (Mollenhoff et al., 2005). In cats undergoing neutering, a single pre-operative dose of IM buprenorphine was compared to pre- and postoperative doses of IM methadone (Bortolami et al., 2013). No cats required rescue analgesia, and there were no variations in mechanical nociceptive thresholds over time in methadone-treated cats, whereas those administered buprenorphine had lower thresholds compared to baseline. In a study of cats undergoing ovariohysterectomy, a single dose of methadone was compared to IM buprenorphine, each combined with medetomidine, ketamine, and midazolam (Shah et al., 2019). Methadone provided lower pain scores over an 8-h postoperative time compared to buprenorphine based on composite pain scale scores, yet superiority or non-inferiority were not addressed (Freise et al., 2013). Taken together, these data support the notion that buprenorphine is a full agonist for the endpoint of pain in cats, with clinical data currently limited to mild to moderate pain, thus precluding a definitive verdict. Nevertheless, these and other data support buprenorphine as an effective analgesic for the control of postoperative pain in cats (see *Clinical Pharmacology in Cats* below).

2.6 | Respiratory

Opioid agonists, such as morphine, are associated with respiratory depression, an adverse reaction that can have serious clinical consequences. The morphine-associated respiratory depression observed in humans also occurs in cats (Etches et al., 1989; Kozaki et al., 2000; Teppema et al., 2008). Respiratory depression ensued when μ-opioid receptor agonist diacetylmorphine was applied directly to the brainstem of anesthetized cats (Taveira da Silva et al., 1983), a site receiving input from central and peripheral chemoreceptors. The hypercapnic stimulus to ventilation through carotid body chemoreceptors is inhibited by μ-opioid receptor agonists in cats (McQueen & Ribeiro, 1980). The role of carotid body opioid receptors remains unclear, but they mediate hypoxic and hypercapnic responses, with their transmission being blocked by opioids at input to the nucleus tractus solitarius in the brainstem (Pattinson, 2008). Opioid respiratory depression has also been associated with κ-opioid receptors in cats, where a κ-opioid receptor antagonist attenuated morphine-induced depression (Kozaki et al., 2000). The integrated mechanism underlying opioid-induced respiratory depression remains elusive. Opioid-induced breathing alterations are complex, regulated by the central and peripheral nervous systems (Etches et al., 1989; Pattinson, 2008) through a variety of opiate receptors (Shook et al., 1990).

The observation that buprenorphine is a partial agonist on the endpoint of respiratory depression, with a ceiling effect (Dahan et al., 2006; Walsh et al., 1994), is consistent with clinical and laboratory observations in cats. When a high-concentration buprenorphine solution was administered SC to healthy cats up to five times the labeled dose for a duration of 9 days, respiratory rates were not altered (Sramek et al., 2015). When TBS was administered to healthy cats up to three times the labeled dose every 4 days over

12 days, respiratory rates remained above the normal range, without clinically relevant changes (Clark, Linton, Freise, Reinemeyer, et al., 2022). In laboratory and clinical studies where buprenorphine was administered with a variety of anesthetics drugs, there was a lack of respiratory depression or clinically meaningful changes in arterial or expired partial pressures of carbon dioxide (pCO_2; Akkerdaas et al., 2001; Bellini et al., 2017; Clark et al., 2022a, 2022b; Grint et al., 2009; Ilkiw et al., 2002; Shah et al., 2019; Warne et al., 2016).

2.7 | Gastrointestinal

The opiate-induced inhibition of gastrointestinal motility was recognized early on, resulting in the development of opiate preparations to treat diarrhea (Campbell, 1971). Opiates decrease propulsive peristaltic contractions, while increasing circular muscle tone and intraluminal pressure (Yaksh & Wallace, 2018). Buprenorphine does induce the gastrointestinal effects observed with full agonists such as morphine. As with respiratory depression, buprenorphine is a partial agonist for gastrointestinal endpoints. Unlike for morphine, early studies of buprenorphine in rodents showed a bell-shaped dose–response curve for gastrointestinal motility inhibition (Cowan, Doxey, & Harry, 1977). In humans, buprenorphine-related constipation occurs in 1%–5% of patients based on longitudinal studies or metanalyses (Evans & Easthope, 2003; Likar et al., 2006; Nasar et al., 1986) and does not result in sphincter of Oddi spasms (Cuer et al., 1989; Staritz et al., 1986).

Several studies in cats demonstrated the minimal gastrointestinal effects of buprenorphine even at high doses. When up to five times the labeled dose of the high-concentration buprenorphine solution was administered SC to healthy 16-week-old cats for a duration of 9 days, there were no differences in food intake, emesis, abdominal palpation, or defecation frequency compared to placebo (Sramek et al., 2015). When TBS was administered to healthy 16-week-old cats up to three times the labeled dose every 4 days over 12 days, the frequency of emesis or constipation was also no different (Clark, Linton, Freise, Reinemeyer, et al., 2022). In another laboratory study of gastrointestinal function, buprenorphine (0.01 mg/kg IM) was co-administered with acetylpromazine (0.1 mg/kg IM), and there were no effects on orocaecal transit times (Sparkes et al., 1996).

2.8 | Behavior

In humans, clinical doses of full opioid agonists, such as morphine, cause mood alterations, sedation, euphoria, and cognitive impairment (Yaksh & Wallace, 2018). In cats, high doses of morphine are associated with behavioral excitement (Fertziger et al., 1974; Huidobro & Lewin, 1969; Loewe, 1956; Sturtevant & Drill, 1957). These behaviors are accompanied by autonomic effects, such as mydriasis, profuse salivation, defecation, urination, and nictitating membrane contraction. High doses of morphine (15–20 mg/kg) in cats have also been associated with aggressive behavior characterized by violent motor excitement (Dhasmana et al., 1972; Fertziger et al., 1974), while smaller doses (5 mg/kg) are associated with sedation and mild excitement (Dhasmana et al., 1972; Wikler, 1944). Cats exhibit well-described behavioral changes even at lower morphine doses (0.5–3 mg/kg; Burgess & Villablanca, 2007). However, the doses of morphine used in these early studies are much higher than the clinically recommended dose in cats (i.e., 0.1–0.3 mg/kg; Robertson & Taylor, 2004) and use of such high doses today would present an animal welfare concern. Mechanistically, microiontophoretically- and pneumatically-applied morphine to Purkinje cells have shown that morphine-induced excitation is connected to the feline opiate system, and inhibition is associated to GABAergic signaling in the cerebellum (Taguchi & Suzuki, 1989).

When cats are administered typical use doses of the full agonist opioids fentanyl, methadone, and morphine, reported behaviors include purring, rubbing, rolling, and kneading (Bortolami et al., 2013; Ferreira et al., 2011; Gellasch et al., 2002; Mahdmina et al., 2020; Robertson, Taylor, Lascelles, & Dixon, 2003; Shah et al., 2019; Steagall et al., 2006). However, in one clinical study, the full agonist levomethadone resulted in central excitation in some cases at the dosage 0.3 mg/kg SC for 5 days in cats undergoing orthopedic surgery (Mollenhoff et al., 2005).

In contrast, previous reviews of buprenorphine described sedation and transient euphoria as the most typical reported behavioral changes in cats (Bortolami & Love, 2015; Steagall et al., 2014). More recently, when high-concentration buprenorphine solutions were administered SC up to 0.24 mg/kg to cats in a laboratory study, euphoria was reported (Doodnaught et al., 2017; Taylor et al., 2016). Even when buprenorphine is administered at multiples of the approved dose, there are limited reports of behavioral excitement in cats. When up to five times the labeled dose of the high-concentration buprenorphine solution was administered SC to healthy 16-week-old cats for a duration of 9 days, two cats experienced hyperactivity, difficulty in handling, disorientation, and agitation (Sramek et al., 2015). When TBS was administered to healthy 16-week-old cats up to three times the labeled dose every 4 days over 12 days, euphoria was described (Clark, Linton, Freise, Reinemeyer, et al., 2022). Euphoria was transient in the first dosing interval, becoming more prolonged with each dosing interval (Figure 3). Although euphoria increased with each interval, dysphoria did not occur at higher doses, as observed for morphine in cats, suggesting that buprenorphine is a partial agonist for the endpoint of behavior. It should be noted that euphoria does not correlate to analgesia, as it does not correlate with laboratory measures of antinociception (Murrell et al., 2007; Steagall et al., 2013). In contrast to laboratory studies, euphoria was not reported in two randomized, placebo-controlled trials with TBS in cats undergoing surgery (Clark et al., 2022a, 2022b). These data suggest that euphoria is less frequent in the presence of pain, similar to opioid-induced respiratory depression being overridden in the presence of pain in humans (Yaksh & Wallace, 2018).

2.9 | Cardiovascular

In humans, morphine induces histamine release from mast cells, resulting in hypotension and blunting reflex vasoconstriction caused by increased pCO_2 (Yaksh & Wallace, 2018). In addition, methadone has been associated with prolonged QTc intervals (Krantz et al., 2009), affecting up to 29% of humans on chronic therapy. Prolonged QTc intervals are associated with torsades de pointes, which is the assumed mechanism of methadone-induced sudden cardiac death (Andrews et al., 2009). In contrast, the risk of cardiac death is fourfold lower for humans maintained on high-dose buprenorphine therapy compared to methadone maintenance (Anchersen et al., 2009).

In cats, morphine has been associated with lower heart rate and hypotension that is responsive to glycopyrrolate (Bauquier, 2012) as well as naloxone-responsive histamine release (Evangelista et al., 2016). Buprenorphine-induced cardiovascular effects have not been observed in cats, nor cardiovascular-related adverse events at clinical doses (Bhalla et al., 2018; Bortolami & Love, 2015; Clark et al., 2022a, 2022b; Evangelista et al., 2017; Mahdmina et al., 2020; Moser et al., 2020; Shah et al., 2019; Steagall et al., 2014, 2018; Warne et al., 2016). In an echocardiographic study evaluating buprenorphine (0.01 mg/kg IM)-dexmedetomidine (0.04 mg/kg IM) sedation in cats, blood pressure increased, and heart rate decreased post-sedation (Johard et al., 2018). Wall thickness and left atrium and aortic diameter were not affected by sedation, but indices of left atrium and left ventricular size increased. The potential for administering this sedation regimen to cats with hypertrophic cardiomyopathy was a primary concern, but since the study was not placebo-controlled, the effects could not be discerned from those of dexmedetomidine administration alone.

In a placebo-controlled laboratory safety study with up to five times the labeled dose of the high-concentration buprenorphine solution administered SC to healthy 16-week-old cats for a duration of 9 days, there were no effects on heart rate, heart rhythm, or blood pressure (Sramek et al., 2015). When TBS was administered to healthy 16-week-old cats at up to three times the labeled dose every 4 days over 12 days, there were no differences in heart rates (Clark, Linton, Freise, Reinemeyer, et al., 2022). Taken together, these data further support the cardiovascular safety of buprenorphine in cats.

2.10 | Thermoregulation

In humans and dogs, full agonist opioids such as morphine tend to cause hypothermia (Kukanich & Papich, 2009; Yaksh & Wallace, 2018). In contrast, mild to moderate hyperthermia in cats has been reported with various opioids, including buprenorphine (Posner et al., 2007, 2010). In cats undergoing ovariohysterectomy that were administered morphine or buprenorphine, the incidence of hyperthermia (>39.2°C) 16–20 h after opioid administration was 56% for morphine and 73% for buprenorphine (Cannarozzo et al., 2020). These changes were rather small, and treatment for hyperthermia was not be necessary.

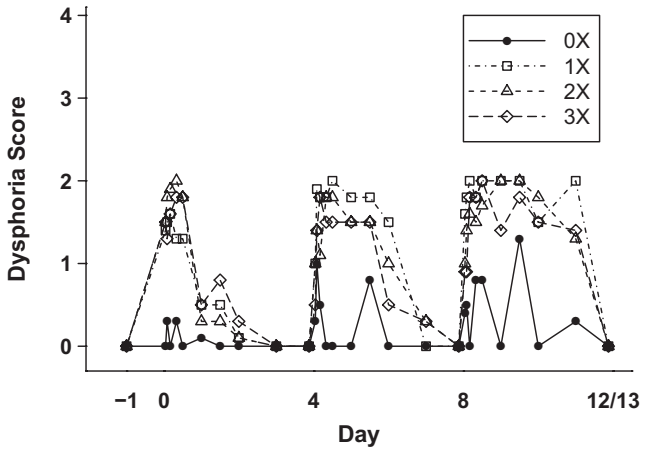


FIGURE 3 Mean behavioral scores following placebo, 1, 2, and 3X dose of TBS administered every 4 days. 0—Normal, 1—Sedated, 2—Euphoric, 3—Mildly dysphoric, 4—Dysphoric. Behavior was assessed at baseline (day −1), prior to each dose administration (0 h), and at 1, 2, 4, 8, 12, 24, 36, 48, and 72 h following treatment on day 0, 4, and 8. From Clark, Linton, Freise, Reinemeyer, et al. (2022)

Increased body temperature has been reported in laboratory and clinical studies for TBS. In a PK study of varying TBS doses, mean temperatures remained 0.6–0.9°C greater than baseline (37.4–37.8°C) through 168 h post-dosing (Freise et al., 2022; Figure 4). Body temperature never reached ≥40.0°C in any individual cat. In a placebo-controlled study of healthy 16-week-old cats, TBS was administered up to three times the labeled dose every 4 days over 12 days, and the mean body temperatures in TBS-treated cats were up to 0.6°C higher, being transient in the first dosing interval, and not rising above normal in subsequent dosing intervals, suggestive of accommodation (Clark, Linton, Freise, Reinemeyer, et al., 2022). In two clinical studies with TBS, postoperative body temperatures were mildly increased over the study duration compared to baseline (Clark et al., 2022a, 2022b). The observed TBS-associated modest increase in body temperature is consistent with that reported for other buprenorphine formulations used in cats and is not considered clinically relevant (Cannarozzo et al., 2020; Posner et al., 2010; Steagall et al., 2014). However, as with other buprenorphine formulations, postoperative monitoring is warranted if interventions are necessary or to differentiate buprenorphine-induced hyperthermia from true fever.

2.11 | Ocular

Full agonist opioids are associated with miosis in humans and dogs (Kukanich & Papich, 2009; Yaksh & Wallace, 2018). In cats, opioid agonists cause mydriasis, and the underlying mechanism of action has been examined for morphine, which activates the oculomotor neurons to induce miosis, but the effect is masked by morphine-induced catecholamine release from the adrenal glands, resulting in mydriasis (Wallenstein & Wang, 1979).

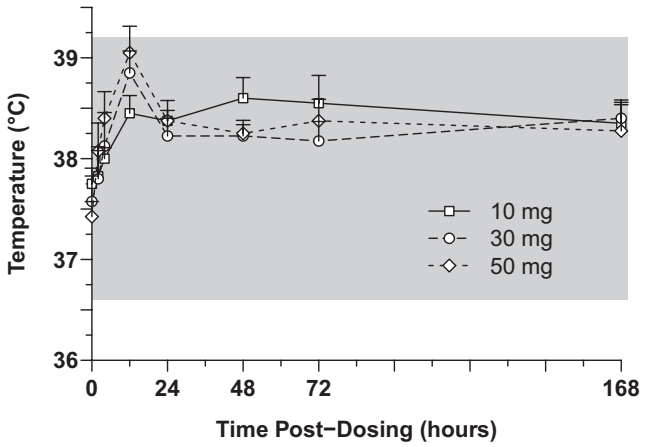


FIGURE 4 Mean rectal body temperatures by dose ($n = 4$ cats per treatment group). Bars indicate the standard error. From Freise et al. (2022)

At clinical doses, mydriasis has been associated with buprenorphine and the mechanism is presumed to be similar to morphine. Mydriasis is not a marker of pain or analgesia (Bortolami & Love, 2015; Steagall et al., 2014). In a clinical study of oral transmucosal (OTM) buprenorphine (20 μg/kg) administered to cats with gingivitis, all cats developed mydriasis within 5 min, persisting for several hours, except in one cat which could not be evaluated owing to bilateral enucleation (Stathopoulou et al., 2018). Protracted mydriasis was reported in a laboratory safety study with high-concentration solution administered to healthy 16-week-old cats (Sramek et al., 2015). In a placebo-controlled laboratory study of healthy 16-week-old cats administered TBS up to three times the label dose every 4 days over 12 days, the proportion of cats with mydriasis was greater than among placebo-treated cats in the first dosing interval and diminished by the third dosing interval, consistent with accommodation (Clark, Linton, Freise, Reinemeyer, et al., 2022; Figure 5).

2.12 | Tolerance and withdrawal

Chronic administration of full agonist opioids leads to a reduced response and the need to increase dosage, collectively referred to as tolerance. In humans, opioid tolerance can lead to opioid rotation whereby a different opioid is selected to regain analgesic activity (Cherny et al., 2001; Chou et al., 2009; Inturrisi, 2002; Pasternak, 2001). The World Health Organization recommends switching opioids for chronic cancer pain if treatment is no longer effective (Likar, 2006). As a consequence of chronic full agonist use, acute withdrawal can lead to a severe affective and clinical syndrome, requiring other opioids to suppress the effects (e.g., methadone; Yaksh & Wallace, 2018).

The examination of morphine tolerance and withdrawal in cats has a long history (Stewart & Rogoff, 1922). Tolerance to the behavioral effects of morphine occurs within 8–10 days following morphine pellet implantation (Huidobro & Lewin, 1969), within 30 days of repeated injections (10 mg/kg/day; Borrell & Borrell, 1975), and within 5 days of repeated injections (5 mg/kg; Cools & van Rossum, 1970). Morphine withdrawal syndrome in cats is characterized by aggressive and irritable behavior (Huidobro & Lewin, 1969) as well as the release of sensory peptides (Morton & Hutchison, 1990; Zhao & Duggan, 1987). Systematic evaluation of buprenorphine tolerance or withdrawal in cats has not yet been performed. This does not present practical concerns as buprenorphine is only approved for the treatment of postoperative pain (Table 2). Depending on the formulation, administration is limited to the day of surgery, repeated daily injections up to 3 days, or a single topical administration that lasts for 4 days. Each of these are acute uses with no supporting data or approval for repeated uses for chronic pain, unlike the case for humans.

2.13 | Clinical pharmacology in cats

2.13.1 | Pharmacokinetics and pharmacodynamics

The PK profiles of various buprenorphine formulations administered via the intravenous (IV), IM, SC, OTM, epidural, and transdermal (i.e., patch) routes have been summarized through 2015 (Bortolami & Love, 2015; Steagall et al., 2014). Some fundamental principles that influence buprenorphine disposition are worth reiterating. Most opioids, including buprenorphine, undergo significant first-pass extraction by the liver when administered orally. Buprenorphine is approximately 10% bioavailable in rats following intraduodenal administration (Brewster et al., 1981b) and is presumed to be similar in cats. Buprenorphine has a low molecular weight of 467.6, a compact molecular structure, high lipid solubility, and adequate water solubility (Johnson et al., 2005), properties that render it ideal for OTM and transdermal delivery (Berti & Lipsky, 1995). Moreover, buprenorphine is a weak base with a pKa of 8.24, and cats have a buccal pH of 8–9 (Robertson et al., 2005; Robertson, Taylor, & Sear, 2003). Thus, a high percentage of the drug exists in the nonionized form, favoring buccal absorption (Robertson, Taylor, & Sear, 2003). When administered OTM to cats, buprenorphine has clinically acceptable bioavailability (Doodnaught et al., 2017; Hedges, Pypendop, Shilo, et al., 2014; Robertson et al., 2005; Robertson, Taylor, & Sear, 2003; Wells et al., 2008) that is reduced in the presence of stomatitis (Stathopoulou et al., 2018). Finally, when PK and PD are examined, the antinociception during the plasma decline phase is greater than that observed when plasma concentrations are rising, demonstrating anticlockwise negative hysteresis (Murrell et al., 2007; Robertson et al., 2005; Steagall et al., 2013). The presumptive mechanism for this observation is a reflection of the time it takes for buprenorphine to distribute to its effect site (i.e., brain and spinal cord) as well as its high affinity and slow off time from opioid receptors (Steagall et al., 2013).

The plasma-concentration time profiles following administration of the low-concentration formulation IV, IM, SC, and OTM are depicted in Figure 6. Reported half-lives after IV, IM, and OTM

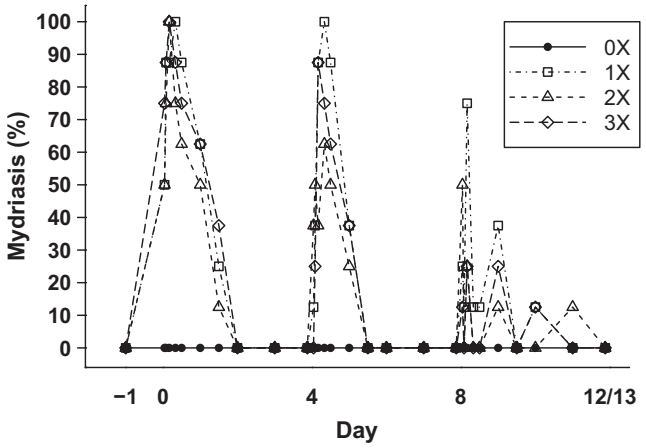


FIGURE 5 Proportion of cats with mydriasis following placebo, 1, 2, and 3X dose of TBS administered every 4 days. Mydriasis was assessed as present or absent (yes/no) at baseline (day −1), prior to each dose administration (0 h), and at 1, 2, 4, 8, 12, 24, 36, 48, and 72 h following treatment on day 0, 4, and 8. From Clark, Linton, Freise, Reinemeyer, et al. (2022).

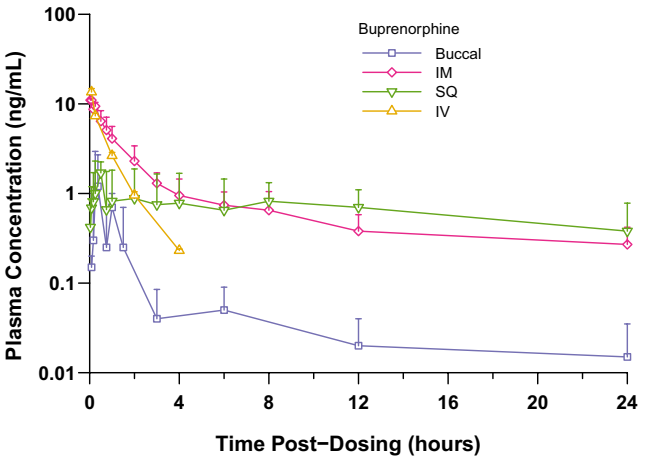


FIGURE 6 Plasma-concentration-time profile following administration of the low concentration buprenorphine solution by OTM (buccal) (Hedges, Pypendop, Shilo-Benjamini, et al., 2014), IM, SC (Steagall et al., 2013), and IV routes Freise et al. (2022)

administration are 1–10 h (Freise et al., 2022; Hedges, Pypendop, Shilo-Benjamini, et al., 2014; Robertson et al., 2005; Steagall et al., 2013; Taylor et al., 2001), 6–8 h (Robertson et al., 2005; Robertson, Taylor, Dixon, et al., 2001; Steagall et al., 2013), and 6–9 h (Hedges, Pypendop, Shilo-Benjamini, et al., 2014; Robertson, Taylor, Bloomfield, & Sear, 2001; Robertson, Taylor, & Sear, 2003), respectively. With the low-concentration formulation, SC PK profiles have been variable (Steagall et al., 2013), and administration via this route is not recommended as it results in reduced antinociception relative to other routes.

A laboratory study in cats examined the low-concentration buprenorphine solution approved for humans (Buprenex™, 0.3 mg/ml) compared to two compounded high-concentration buprenorphine solutions (0.6 and 1.2 mg/ml), with and without preservatives (Taylor et al., 2016), each administered SC. There was an anticlockwise negative hysteresis loop (Figure 7), and the authors proposed a half-maximal effective analgesic plasma concentration (EC50) of 2.3 ng/ml based on the offset concentration. These data support high-concentration solutions administered via SC injections and provide a contrast to the variability and apparent ineffectiveness of low-concentration formulations administered SC.

A joint PK-PD model of the FDA-approved high-concentration buprenorphine solution ('Simbadol; Zoetis') was constructed based on a thermal threshold laboratory study in cats (Doodnaught et al., 2017). Cats were administered the formulation via SC (0.24 mg/ml), IV (0.12 mg/kg), or OTM (0.12 mg/kg) routes, and thermal thresholds were compared to a negative control (i.e., saline). The PK of buprenorphine and norbuprenorphine following the 0.24 mg/kg SC dose is depicted in Figure 8. Bioavailability via the OTM route was approximately 24%. Using a bespoke joint population PK and PK-PD model, the duration-of-action of the approved formulation was supported. At the approved dose, SC injection resulted in antinociception of ≥24 h, whereas IV and OTM routes were approximately 8 h.

In laboratory cats, the PK of an investigational liposome-encapsulated formulation containing approximately 1.75 mg/ml buprenorphine administered SC (0.2 mg/ml) was compared to the approved buprenorphine solution (0.3 mg/ml) administered IV (Johnson et al., 2017). Plasma buprenorphine concentrations for the investigational formulation were above 0.5 ng/ml for more than 96 h, with three distinct peaks in the first 15 h. The buprenorphine EC_{50} has been proposed to be 2.3 ng/ml based on the offset concentrations (Taylor et al., 2016) and thus it is not certain how time above 0.5 ng/ml relates to antinociception. Therefore, liposomes prolong buprenorphine systemic exposure, but the formulation has not been further systematically developed.

For the newly approved TBS, PK has been described in laboratory cat studies. The plasma-concentration time curve from cats weighing 2.35–6.35 kg administered 10, 30, or 50 mg of TBS is depicted in Figure 9 (Freise et al., 2022). Plasma buprenorphine reached mean peak concentrations between 2- and 4-h post-dosing, and all samples remained above the lower limit of quantitation through 168 h. The mean terminal half-lives ranged from 78.3 to 91.2 h, consistent with absorption-dependent kinetics (i.e., flip-flop). There were 2.8- and 3.6-fold increases in the area under the plasma-concentration time curve from time 0 to infinity ($AUC_{0-\infty}$) in the 30 and 50 mg dose group, respectively, compared to the 10 mg group, consistent with a lack of dose proportionality at above 30 mg. The estimated absolute bioavailability of the approved dose was 16.0% (90% CI: [11.8%–21.7%]; Figure 10). When one, two, and three times the approved dose were administered every 4 days for a total of three doses, drug accumulation was estimated (Figure 11; Clark, Linton, Freise, Reinemeyer, et al., 2022). The simulated drug exposure relative to the area under the plasma-concentration time curve for the 1X dose during the first dosing interval (AUC_{0-96}) was 1.79, 3.59, and 5.38 in the 1, 2, and 3X groups, respectively, by the third dosing interval.

The above-described PK with TBS can be contrasted to those in an earlier laboratory study of transdermal buprenorphine patches

applied to cats (Murrell et al., 2007). Transdermal matrix buprenorphine patches have been approved in Europe (Transtec; 'Napp Pharmaceuticals)) and USA (Butrans Transdermal System; Purdue Pharma L.P. 2010) for chronic but not postoperative pain in humans. They are available in strengths designed to deliver zero-order transdermal buprenorphine at the nominal rate identified on the patch, ranging from 5 to 70 μg/h. When a 35 μg/h patch was applied to the clipped thorax of cats in a laboratory study, there was no significant change in thermal thresholds despite a slow rise in plasma buprenorphine concentrations (Murrell et al., 2007).

2.13.2 | Clinical evidence

The medical benefits of opioids, particularly buprenorphine, for pain management in cats have been reviewed through 2015 (Bortolami & Love, 2015; Steagall et al., 2014). To integrate this information in the context of new advances, some key concepts will be reiterated. Since 2015, several clinical studies evaluated buprenorphine in cats, and the key results are summarized in Table 8.

In controlled clinical studies, a single IM or IV administration of the low-concentration buprenorphine solution at doses ranging from 6–20 μg/kg is an effective preoperative analgesic in cats undergoing various soft tissue and orthopedic surgeries (Dobbins et al., 2002; Giordano et al., 2010; Polson et al., 2012; Slingsby & Waterman-Pearson, 1998; Stanway et al., 2002, 1996; Taylor et al., 2010). However, there are conflicting data on its effectiveness as a single injection. One study reported that a single preoperative buprenorphine administration (20 μg/kg IM) in combination with medetomidine was not sufficient to control pain associated with ovariohysterectomy and additional administrations were necessary (Warne et al., 2014).

The idea to evaluate OTM buprenorphine in cats originated from the successful use of sublingual transmucosal tablets in humans ('Temgesic Sublingual Tablets; (Indivior UK Limited' 1980). Administration via this route to cats utilizes injectable buprenorphine solution or compounded formulations from injectable buprenorphine solution or sublingual tablets. A single OTM dose has a duration-of-action similar to a single IV or IM injection of low-concentration solution (Lascelles et al., 2003; Porters et al., 2014; Robertson et al., 2005). Clinical efficacy varies, with some reporting inferior efficacy compared to parenteral administration (Catbagan et al., 2011; Gassel et al., 2005; Giordano et al., 2010). When OTM buprenorphine is co-administered with an α-2 agonist, sedation results vary (Porters et al., 2014; Santos et al., 2010).

Other compounded investigational formulations have been evaluated in clinical studies in an attempt to extend the duration-of-action. A proprietary matrix sustained-release injectable buprenorphine was reported to extend the analgesic duration-of-action for several days in cats undergoing ovariohysterectomy (Catbagan et al., 2011). It was concluded that the compounded product was equivalent to OTM buprenorphine. However, pain variables were compared via post-hoc *t* tests, but comparable efficacy (i.e., noninferiority) cannot be concluded unless the effect size for the control is known (i.e., compared to placebo) and a zone of indifference is declared a priori (Freise et al., 2013). Another compounded extended-release buprenorphine formulation was evaluated in cats undergoing unilateral onychectomy (Enomoto et al., 2016). When administered prior to surgery, there was a positive influence on subjective pain scores over 72 h, no cats required pain interventions, and there was decreased limb asymmetry when landing or walking on a pressure-sensitive walkway. Although promising, these compounded products are considered investigational and are not developed through good manufacturing practices to ensure identity, strength, quality, purity, and safety ("21 CFR 514.1 Manufacturing methods, facilities, and controls" [U.S. Department of Health and Human Services, 2008]).

The high-concentration injectable buprenorphine solution has been shown as effective in laboratory and clinical studies. In a PK-PD model that integrated PK and thermal threshold antinociception PD, the duration-of-action of a single injection was shown to be ≥24 h (see *Pharmacokinetics and Pharmacodynamics* above; Doodnaught et al., 2017). In a placebo-controlled field study, the high-concentration injectable solution was administered once prior to surgery and for two additional days to 221 cats undergoing ovariohysterectomy, various soft tissue surgeries, and onychectomy ('Simbadol; Zoetis'). Using an interactive pain scale, cats judged to have inadequate pain control were administered rescue analgesia. The dropout rates (i.e., cats that required rescue analgesia) for placebo- and buprenorphine-treated cats were 55.9% and 29.0%, respectively. Of the 56 cats rescued in the placebo group, 51 were rescued in the first 4 h of recovery. Of the 27 cats rescued in the buprenorphine group, 24 were rescued in the first 4 h of recovery. There were five placebo- and three buprenorphine-treated dropouts from 4 h after surgery until the end on day 3. As observed for other buprenorphine formulations, postoperative body temperatures were increased but were not considered clinically meaningful. These data contributed to FDA approval of the high-concentration buprenorphine solution, labeled for the control of postoperative pain associated with soft tissue surgery to be administered daily for three injections, with the first dose administered approximately 1 h prior to surgery.

In a recent study, the potential benefit of follow-on hydromorphone treatment after high-concentration buprenorphine solution administration ('Simbadol; Zoetis') was evaluated in a laboratory thermal threshold model in cats (Moreno et al., 2021; Table 8). In a randomized, blinded, placebo-controlled crossover laboratory study, cats were allocated to saline control, high-concentration buprenorphine solution (0.24 mg/kg SC), or high-concentration buprenorphine solution followed by hydromorphone 2 h later (0.1 mg/kg IV). Thermal thresholds were significantly higher than saline over 3–18 h and 4–12 h for buprenorphine and buprenorphine-hydromorphone, respectively. These data show that administration of IV hydromorphone following high-concentration buprenorphine provides no additional antinociception and decreases the duration of effect when compared with high-concentration buprenorphine alone. When

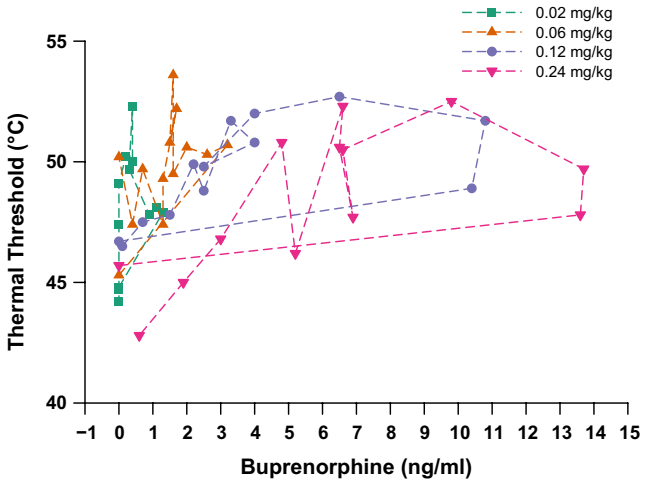


FIGURE 7 Plasma buprenorphine concentration thermal threshold hysteresis loops from cats after subcutaneous injection of investigational high concentration buprenorphine solution at doses of 0.02, 0.06, 0.12, and 0.24 mg/kg. All loops are anticlockwise. From Taylor et al. (2016)

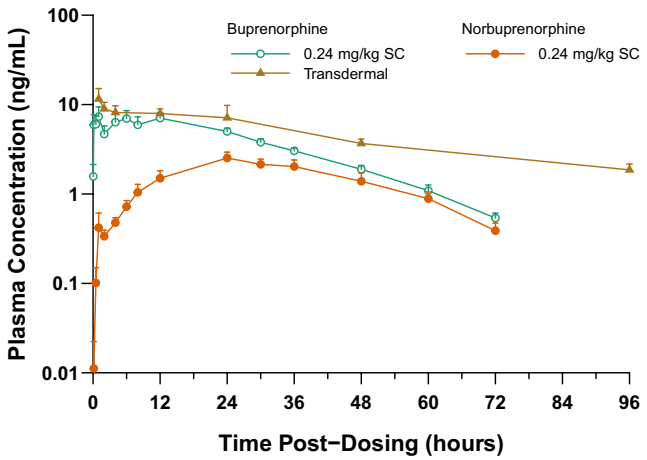


FIGURE 8 Buprenorphine and norbuprenorphine plasma-concentration-time profile following SC administration of the high concentration buprenorphine solution (Doodnaught et al., 2017) and the buprenorphine plasma-concentration-time profile following a single topic dose of TBS (Freise et al., 2022)

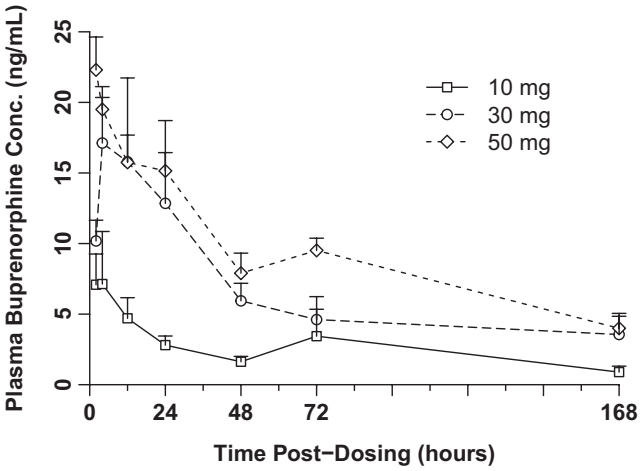


FIGURE 9 Mean plasma buprenorphine concentrations following a 10, 30, or 50 mg single dose of TBS in cats weighing between 2.35 to 6.35 kg ($n = 4$ cats per treatment group). Bars indicate the standard error. From Freise et al. (2022)

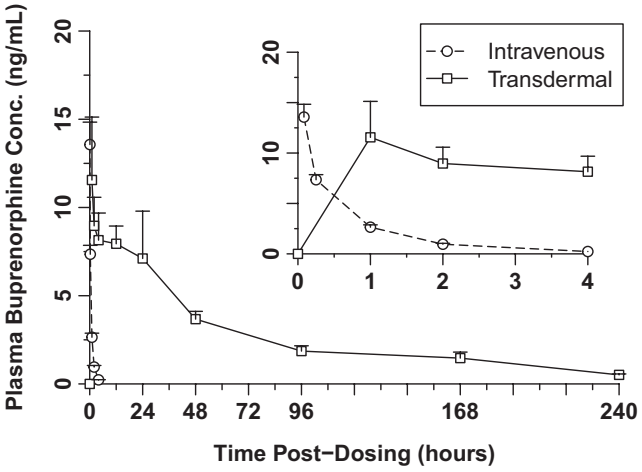


FIGURE 10 Mean plasma buprenorphine concentrations following a 20 mg dose of TBS or 0.05 mg dose of IV buprenorphine solution (0.3 mg/ml) administered to cats weighing between 4.2 to 6.35 kg ($n = 6$ cats per treatment group). Bars indicate the standard error. Inset expands the *x*-axis over the first 4 h. From Freise et al. (2022)

additional analgesia is required after the administration of high-concentration buprenorphine, alternative analgesics should be considered. This is likely generalizable to all buprenorphine formulations.

Most recently, TBS was approved by the FDA. Based on the outcome of PK laboratory studies that identified candidate doses (Freise et al., 2022), a multi-centered phase 2 clinical study was conducted to determine an appropriate dose for a larger phase 3 study (Clark et al., 2022a). One-hundred and six healthy cats undergoing ovariohysterectomy or orchiectomy, both in conjunction with onychectomy, were randomized to three preoperative treatments: topical placebo, low-dose TBS 2–4 h prior to anesthetic induction (i.e., 4 mg for cats 1.2–3 kg and 10 mg for cats >3–7.5 kg), or high-dose TBS 1–2 h prior to anesthetic induction (i.e., 8 mg for cats 1.2–3 kg and 20 mg for cats >3–7.5 kg). Preoperative IM dexmedetomidine was administered to all cats, and, following anesthetic induction, a lidocaine metacarpal 4-point ring block on the forelimbs was conducted (Skarda & Tranquilli, 2007). Postoperatively, interactive pain assessments were conducted based on a modification by King et al. (2012) and similar to those used in the high-concentration injectable buprenorphine solution clinical study ('Simbadol; Zoetis'), to a binary endpoint of adequate or inadequate pain control. The FDA-approved dose of butorphanol (0.4 mg/kg SC) was immediately administered to cats considered to experience inadequate pain control. Following rescue, butorphanol or other analgesic drugs could be administered as needed. Treatment failure was recorded for 31 (89%), 16 (46%), and 12 (33%) cats in the placebo-, low-, and high-TBS dose groups,

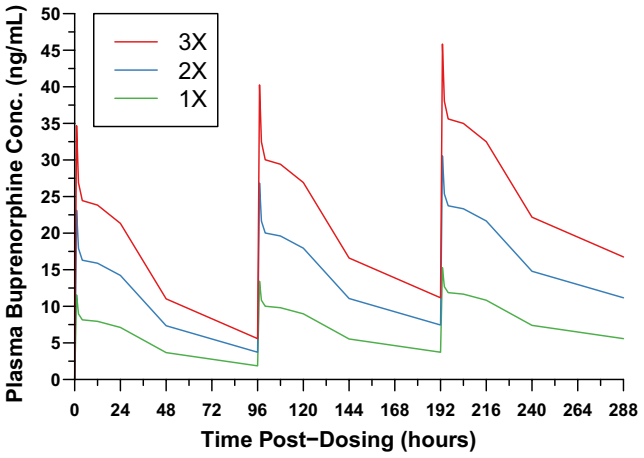


FIGURE 11 Simulated buprenorphine plasma concentration-time data over when 1, 2, and 3X the approved dose of TBS is administered every 4 days for three doses. From Clark, Linton, Freise, Reinemeyer, et al. (2022)

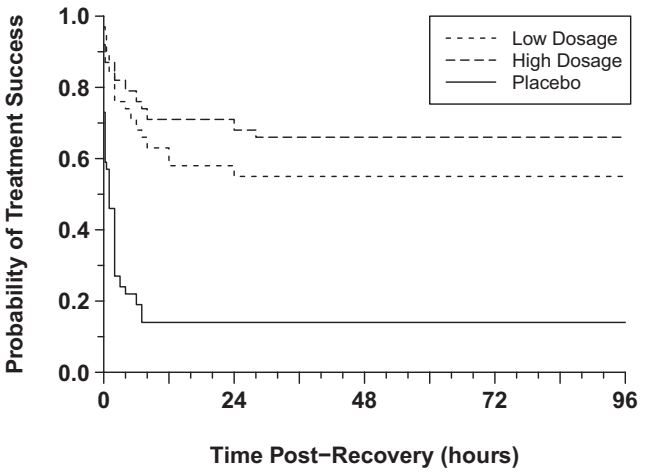


FIGURE 12 Kaplan–Meier curve of probability of treatment success from postoperative recovery time (i.e., sternal recumbency = time 0) through 96 h for placebo and low- and high-dose TBS in a phase 2 dosage characterization controlled clinical study. From Clark et al. (2022b)

respectively. The estimated overall treatment success rates from the generalized linear mixed model (GLMM) analysis were 0.10 (95% CI: [0.02–0.37]), 0.56 (95% CI: [0.28–0.80]), 0.71 (95% CI: [0.41–0.88]) in the placebo-, low-, and high-TBS dose groups, respectively. Most treatment failures occurred on the day of surgery, with all failures in the placebo group occurring within the first 7 h following anesthetic recovery (i.e., sternal recumbency; Figure 12). The high-TBS dose was selected for further evaluation in a larger phase 3 clinical study (Clark et al., 2022b).

An additional outcome of the phase 2 study was supportive data for the development of unit dosing applicator tubes. Cats generally have a narrow body weight range, which allows for unit dosing. Body weights in the phase 2 study had a mean of 3.0 (range: [1.6–4.8]) kg. With this outcome, unit dose applicator tubes were developed to deliver 8 mg (0.4 ml) and 20 mg (1 ml) of buprenorphine to smaller and larger cats, respectively, from a 20 mg/mL solution (Table 9 and Figure 13).

In a follow-up multi-centered phase 3 clinical study conducted with TBS, 228 cats undergoing ovariohysterectomy or orchiectomy, both in conjunction with onychectomy, were randomized to two preoperative treatments: topical placebo or TBS 1–2 h prior to anesthetic induction (i.e., 8 mg for cats 1.2–3 kg and 20 mg for cats >3–7.5 kg) with single-use applicator tubes (Figure 13). Design and analysis were similar to those of the phase 2 study. A total of 65 (60.7%) placebo-treated cats were considered treatment failures due to inadequate pain control in contrast to 23 (20.5%) for TBS. The overall treatment success rates estimated via GLMM analysis were 0.40 (95% CI: [0.28–0.53]) and 0.81 (95% CI: [0.70–0.89]) for placebo- and TBS-treated cats, respectively. Most treatment failures occurred on the day of surgery (Figure 14). These data contributed to the FDA approval of TBS for the control of postoperative pain associated with surgical procedures in cats, where a single topical dose is applied 1–2 h prior to surgery, providing analgesia for 4 days.

In a pivotal clinical trial to confirm the effectiveness of an investigational drug, an active (i.e., positive) control may be considered when a drug of the same class is approved in the same species for the same indication for the same duration. The two other approved drugs for the control of postoperative pain in cats (Onsior; '(Elanco 2011)'; 'Simbadol; Zoetis') are labelled for an initial preoperative dose and two daily follow-up doses. To ensure assay sensitivity with a potential active control (Freise et al., 2013), there must be one or more, well-powered, placebo-controlled studies using the same clinical assessment method and endpoint so that a non-inferiority margin (i.e., zone of indifference) can be calculated. Moreover, even when a prior placebo-controlled study with an active control is available, a placebo-control arm may be included along with an active control arm out of concern for trial sensitivity. That is, if the active control is not superior to placebo within the trial of the investigational drug, the investigational drug would be declared non-inferior to an ineffective drug. Approval and subsequent wide clinical use of an ineffective treatment introduces a broad ethical dilemma. To increase the degree of confidence in the approval decision regarding treatment effectiveness, placebo-controlled, superiority trials are generally conducted. In addition to TBS, numerous analgesics for dogs and cats have been developed under this framework where placebo-controlled studies were conducted to evaluate effectiveness ('Rimadyl; (Zoetis 1996)'; 'Etodolac; (Fort Dodge 1998)'; 'Deramaxx; (Elanco 2002)'; 'Onsior; Elanco'; 'Simbadol; (Zoetis)'; 'Solensia; (Zoetis)'; Rausch-Derra et al., 2016; King et al., 2012).

A potential limitation of the two randomized controlled studies that examined the dosage and effectiveness of TBS is that a validated pain scale that underwent a priori evaluation of content, criterion, construct, responsiveness, and reliability was not used (Cook & Beckman, 2006; Streiner & Norman, 2008). The interactive pain assessment method used in the two TBS clinical studies was similar to that used for the approval of the high-concentration

TABLE 8 Clinical studies evaluating buprenorphine in cats, published since 2015

Procedure	N	Treatments	Assessment	Results	Conclusions	References
Clinical study: randomized, negative controlled, blinded, OVH	12	20 μg/kg IM buprenorphine and alfaxalone 3.0 mg/kg (SC). Postoperatively allocated to: 1. Atipamezole 2. Saline	A validated multidimensional composite scale	The postoperative pain scores for the atipamezole group were not significantly different from the saline group. The post-rescue pain scores for the atipamezole group were not significantly different from the saline group.	Atipamezole did not significantly affect the postoperative pain scores. Premedication with buprenorphine did not provide adequate postoperative analgesia.	Warne et al. (2016)
Laboratory study: randomized, crossover, blinded, negative controlled, unilateral onychectomy	4	Saline or investigational extended-release buprenorphine (ER-Bup) 0.6 mg/kg (SC) 20–60 min prior to anesthetic induction	Pressure-sensitive walkway and subjective pain scores	No cats required rescue analgesics. ER-Bup had a positive influence on subjective pain scores during over 72 h. Peak vertical force and vertical impulse were decreased for both landing and walking compared to control. ER-Bup resulted in decreased asymmetry in limb use during landing and walking.	SC administration of ER-Bup may be an effective analgesic for a 72 h period postoperatively. Landing onto a pressure-sensitive walkway from an elevated perch may be a useful and efficient way to assess analgesics in cats using a unilateral model of limb pain.	Enomoto et al. (2016)
Laboratory study: randomized, crossover, blinded, negative controlled, sciatic and femoral nerve blockade	6	Dexmedetomidine (25 mg/kg, IM) sedation and sciatic and femoral nerve blockade with: 1. Saline 2. Bupivacaine 3. Bupivacaine plus dexmedetomidine 4. Bupivacaine plus buprenorphine (2.5 μg/kg) Post injection, atipamezole	Paw withdrawal thresholds (PWT) and motor blockade were evaluated before sedation and up to 24 h	Compared with saline, PWT were significantly increased in bupivacaine (from 1 to 6 h), bupivacaine plus dexmedetomidine (at 2 and 3 h), and in bupivacaine plus buprenorphine (at 2 and 3 h)	Bupivacaine plus dexmedetomidine or bupivacaine plus buprenorphine did not increase PWT or prolong the duration of motor blockade when compared with bupivacaine alone.	Evangelista et al. (2017)
Clinical study: prospective, blinded, active controlled, sedative effects for IV catheter placement	40	1. Butorphanol plus dexmedetomidine 2. Buprenorphine (20 μg/kg IM) plus dexmedetomidine	Multidimensional composite scale	In both groups, sedation scores changed over time, and the highest sedation scores were reached at 10 min but higher in the butorphanol plus dexmedetomidine group at 5, 10, 15, and 20 min. Requirement for additional sedation was similar between groups	Butorphanol–dexmedetomidine may be preferred for sedation, especially where vomiting is contraindicated	Bhalla et al. (2018)
Clinical study: prospective, negative controlled, blinded, crossover of analgesic effect and absorption after buccal administration in cats with chronic gingivostomatitis	6	Day 1, pain scores, dental examination, stomatitis score, and buccal pH measurement were conducted under sedation in all cats. Day 2 treatment: 1. Buprenorphine (20 μg/kg, OTM) 2. Saline Day 3, crossover treatments.	Collect blood samples and score pain by modified Botucatu pain at 30, 90, and 360 min	Maximum buprenorphine plasma concentration was reached 30 min after administration, and there was low inter-individual variability. There was a significant difference in pain scores between the saline and buprenorphine group at 30 and 90 min	OTM buprenorphine in cats with gingivostomatitis produces an analgesic effect and low inter-individual variability in plasma concentration, and it can be incorporated in multimodal analgesia plan	Stathopoulou et al. (2018)

TABLE 8 (continued)

Procedure	N	Treatments	Assessment	Results	Conclusions	References
Clinical study: active controlled, blinded, analgesic effects in OVH, using two pain-scoring systems	52	Acepromazine-buprenorphine (20 μg/kg IM)-propofol-isofluorane anesthesia. Treatments: 1. Gabapentin plus buprenorphine (20 μg/kg, IM). 2. Meloxicam plus buprenorphine (20 μg/kg, IM) plus placebo capsules 3. Buprenorphine (20 μg/kg, IM) and placebo capsules	Pain assessed for 8 h post-surgery using multidimensional composite pain scale (MCPS) and the Glasgow pain scale (rCMPS-F). Sedation assessed by dynamic interactive visual analog scale (DIVAS)	The prevalence of rescue analgesia was not different among treatments. A strong correlation was observed between scoring systems	Analgesia was not significantly different despite a strong correlation between scoring systems, gabapentin plus buprenorphine and meloxicam plus buprenorphine would have been superior to the buprenorphine alone with the rCMPS-F demonstrating a potential type II error with an MCPS due to small sample size	Steagall et al. (2018)
Clinical study: assessor-blinded, active controlled, analgesic efficacy following OVH	120	1. Methadone 2. Buprenorphine (180 μg/m^2) Each treatment included ketamine, midazolam, and medetomidine.	Pain assessed by Composite Measure Pain Scale (CMPS-F), a dynamic interactive visual analogue scale (DIVAS) and mechanical nociceptive threshold (MNT)	Methadone had lower CMPS-F scores over time. Eighteen of 60 cats required rescue analgesia in the methadone group versus 29/60 in the buprenorphine group. All cats that received rescue analgesia required it within 6 h post-QUAD administration. There were no differences between groups in MNT or pain measured using the DIVAS	Methadone lower pain scores for the first 8 h after neutering compared to a single buprenorphine injection when used within the QUAD protocol.	Shah et al. (2019)
Clinical study: assessor blinded, quality of anesthesia and analgesia of two treatments in OVH	51	Premedication: 1. Medetomidine plus buprenorphine (180 μg/m^2 IM) 2. Medetomidine and methadone Anesthesia induced with alfaxolone maintained with isoflurane Meloxicam and atipamezole postoperatively	Pain assessments by simple descriptive scale, numeric rating scale, dynamic interactive visual analogue scale (DIVAS) and UNESP-Botucatu multidimensional composite pain scales	Forty-one cats completed the study. No significant differences were detected between groups before or during anesthesia. No cats required rescue analgesia	Methadone and buprenorphine combined with medetomidine provided safe and stable sedation the plane of anesthesia was suitable for carrying out invasive surgery perceived to cause moderate pain	Mahdmina et al. (2020)

(continues)

TABLE 8 (continued)

Procedure	N	Treatments	Assessment	Results	Conclusions	References
Clinical study: prospective, blinded, active controlled, orchiectomy	47	Treatments: 1. Butorphanol 2. Buprenorphine (20 μg/kg IM). Both treatments combined with dexmedetomidine and alfaxalone for the induction of general anesthesia. Postoperatively, lidocaine (2 mg/kg intratesticular), meloxicam and atipamezole	Pain assessed by UNESPBotucatu multidimensional composite pain scale (UB MCPS) and the revised composite measures pain scale—feline (RCMPSF)	No difference in sedation or pain scores. Four cats required rescue analgesia (butorphanol, $n = 3$; buprenorphine, $n = 1$). More cats in the buprenorphine group ($n = 12$) required isoflurane than in the butorphanol group ($n = 2$). No differences in time to achieve sternal recumbency or return to eating	Inclusion or butorphanol or buprenorphine in a multimodal analgesia protocol provides similar analgesia outcomes but butorphanol may result in less need for gas anesthetic	Moser et al. (2020)
Laboratory study: randomized, blinded, placebo-controlled crossover	6	Treatments (injections separated by 2 h): 1. Saline SC then saline IV (SS) 2. Buprenorphine (1.8 mg/ml) SC (0.24 mg/kg) followed by saline IV (BS) 3. Buprenorphine (1.8 mg/ml) SC followed by hydromorphone IV (0.1 mg/kg; BH)	Skin temperature (ST) and thermal threshold (TT) were recorded before (baseline) and for 24 h following first injection	Compared with baseline, TT was significantly increased at all time points in treatments BH and BS except at 2 h in treatment BS. TT was significantly higher than SS at 3–18 h and 4–12 h for treatments BS and BH, respectively. Maximal increases in TT were 47.5°C at 2 h, 53.9°C at 3 h and 52.4°C at 6 h in treatments SS, BS, and BH, respectively	Administration of IV hydromorphone following high-concentration buprenorphine provided no additional antinociception and decreased the duration of effect when compared with high-concentration buprenorphine alone. Alternative analgesics should be considered if additional analgesia is required after administration of high-concentration buprenorphine	Moreno et al. (2021)

TABLE 9 Transdermal buprenorphine solution dosing table

Pounds of body weight	Kilograms of body weight	Dose of TBS (Zorbium™)
2.6–6.6	1.2–3	0.4 ml (8 mg) pink tube
>6.6–16.5	>3–7.5	1 ml (20 mg) green tube

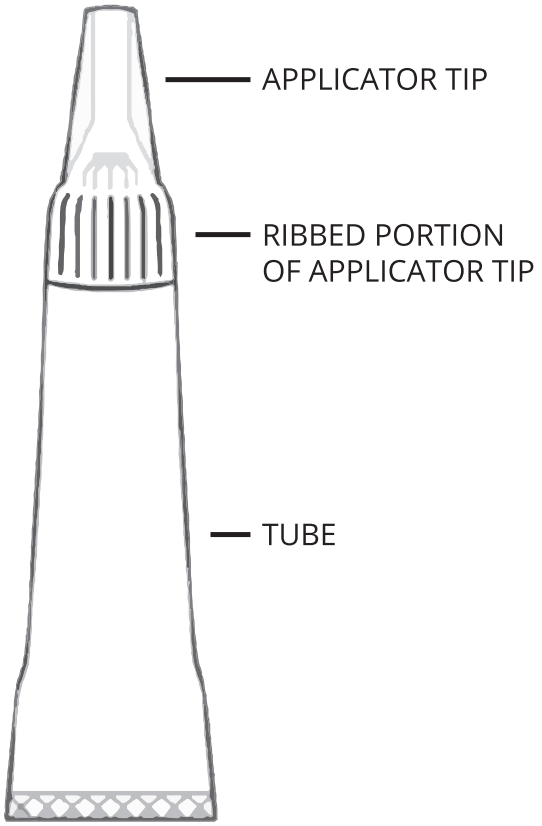


FIGURE 13 Unit dose applicator tubes were developed to deliver 8 mg (0.4 ml) and 20 mg (1 ml) of buprenorphine to smaller (1.2–3 kg) and larger (>3–7.5 kg) cats, respectively, from a 20 mg/ml solution

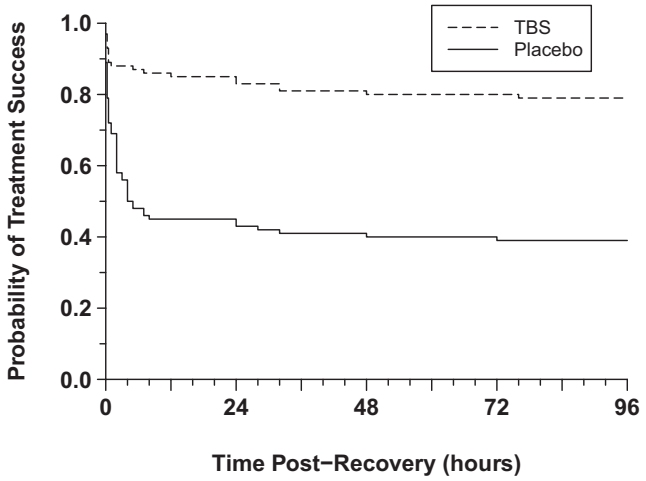


FIGURE 14 Kaplan–Meier curve of probability of treatment success from postoperative recovery time (i.e., sternal recumbency = time 0) through 96 h for placebo and TBS in a phase 3 pivotal randomized controlled clinical study. From Clark et al. (2022b)

buprenorphine solution and robenacoxib (King et al., 2012; 'Onsior Elanco'; ('Simbadol;)'). Out of concern for trial assay sensitivity and constancy (Freise et al., 2013), trials intended for FDA submission tend to use similar outcome measures. In a placebo-controlled study with robenacoxib in cats undergoing onychectomy/ovariohysterectomy or onychectomy/castration, the dropout rates for placebo and robenacoxib were 46.3% and 16.5%, respectively ('Onsior; Elanco'; King et al., 2012). In a placebo-controlled study with the high-concentration buprenorphine solution in cats undergoing various surgeries, the dropout rates for placebo and treatment were 55.9% and 29.0%, respectively ('Simbadol; Zoetis'). These four independent controlled clinical studies demonstrate assay sensitivity, constancy, and the utility of the employed pain assessment scale. Differentiating treatments using similar pain assessment scales in these four independent trials would not occur by random chance alone. Had the method lacked the capacity to detect pain when pain was present, there would have been few dropouts and a lack of significance. Alternatively, had the pain assessment method overestimated the presence of pain when pain was absent, there would have been too many dropouts and a lack of significance.

The selection of butorphanol as a rescue drug in the two TBS clinical trials was due to the need to use a drug according to label. Butorphanol is approved for pain associated with surgical procedures at a dose of 0.4 mg/kg administered SC. The two other FDA approved drugs for the control of postoperative pain in cats ('Onsior; Elanco'; 'Simbadol; Zoetis') are indicated for an initial preoperative dose and two daily follow-up doses. The onset- and duration-of-action of butorphanol has been examined alone or in combination with buprenorphine. In a PK-PD thermal threshold study in cats, 0.2 mg/kg IM butorphanol, 0.02 mg/kg IM buprenorphine solution (Buprenex, 0.3 mg/ml) and their coadministration were evaluated (Johnson et al., 2007). Butorphanol, buprenorphine, and butorphanol-buprenorphine combination induced a significant increase in thermal thresholds compared with pretreatment values from 50 min to 8 h, from 35 min to 5 h, and from 50 min to 8 h, respectively.

Taken together, buprenorphine has been adapted for use in feline medicine, resulting in the approval of low- and high-concentration injectable solutions, and, most recently, a long-acting transdermal formulation. Several investigational and compounded formulations have also been evaluated. There are contrasting differentiable features that include PK, onsets- and durations-of-action, and routes of administration. The buprenorphine formulations available allow clinicians to select the most appropriate based on the anticipated duration of pain associated with various surgical procedures, and to provide interventions as needed.

2.13.3 | Metabolism

Buprenorphine metabolism has been extensively described in humans. Once absorbed, 96% is bound to α-globulin and β-globulin fractions, rather than albumin (Heel et al., 1979). Rapid metabolism of buprenorphine through N-dealkylation in the liver produces norbuprenorphine (Huang et al., 2001) through a reaction catalyzed by CYP3A4 (65%) and CYP2C8 (30%; Iribarne et al., 1997; Kobayashi et al., 1998; Picard et al., 2005). Parent compound and metabolites undergo phase II metabolism by uridine 5′-diphospho-glucuronosyltransferase (UGT; Cone et al., 1984). Buprenorphine and norbuprenorphine undergo glucuronidation by UGT1A1 (King et al., 1996) and also by UGT2B7 and UGT1A3, respectively (Chang & Moody, 2009; Green et al., 1998; Rios & Tephly, 2002). Buprenorphine and its metabolites are excreted in urine and feces (Cone et al., 1984).

Buprenorphine metabolism in cats has not been comprehensively characterized although norbuprenorphine in plasma has been detected. Following the administration of high-concentration buprenorphine solution SC (0.24 mg/kg), IV (0.12 mg/kg), or OTM (0.12 mg/kg) to cats, norbuprenorphine was quantifiable through 72 h (Figure 8; Doodnaught et al., 2017). In another study, norbuprenorphine was not detected following IM or OTM buprenorphine administration (Porters et al., 2015). In a third study of varying doses of buprenorphine administered to cats, the authors reported the ratio of norbuprenorphine to buprenorphine (Taylor et al., 2016). For cats that received a dose of 0.12 mg/kg, the ratio of norbuprenorphine to buprenorphine was 0.35 ± 0.33, whereas for the 0.24 mg/kg dose, it was 0.40 ± 0.18. Comparable ratios in rhesus macaques, dogs, and humans were 0.13, 0.09, and 2.73, respectively (Abbo et al., 2008; Andaluz, Moll, Abellan, et al., 2009; Andaluz, Moll, Ventura, et al., 2009; Huang et al., 2006; Nunamaker et al., 2013). Therefore, cats appear to be able to metabolize buprenorphine to norbuprenorphine similarly to dogs and monkeys, but probably to a lesser extent than humans. These results also suggest that buprenorphine is metabolized by a cat homolog of human CYP3A, which is yet to be identified in cats (Trepanier, 2006). Evidence for CYP3A in cat liver microsomes is indirect, where the oxidation of 7-benzyloxy-4-(trifluoromethyl)-coumarin (BFC) was reduced by addition of the CYP3A inhibitor, ketoconazole (van Beusekom et al., 2010).

2.13.4 | Pharmacogenomics

Pharmacogenomic targets of buprenorphine associated with its PD and metabolic profile in humans include the genes coding for μ-, δ-, and κ-opioid receptors, in addition to metabolism-associated genes encoding cytochrome P450 enzymes and UGTs. The clinical implications for each polymorphism in humans have been reviewed (Meaden et al., 2021; Sadhasivam & Chidambaran, 2012).

The μ-opioid receptor gene OPRM1 has several polymorphisms associated with an inconsistent opioid response (Lotsch et al., 2004) and variable addiction risk (Goldman et al., 2005). In a human clinical study, buprenorphine-treated subjects carrying the OPRM1 118 G polymorphism had a reduced hypothalamic–adrenal–pituitary axis response compared to 118 A carriers (Kakko et al., 2008), suggesting that the OPRM1 118 G polymorphism could confer a poorer response to buprenorphine. The δ-opioid receptor gene OPRD1 has been shown to have several polymorphisms associated with varying risks of opioid dependence (Levran et al., 2008; Mayer et al., 1997; Zhang et al., 2008), predictive of buprenorphine treatment outcomes (Crist et al., 2013, 2019). Finally, a SNP in OPRK1 was described as associated with addiction treatment outcomes (Gerra et al., 2014).

The primary hepatic cytochrome P450 involved in buprenorphine phase I metabolism in humans is CYP3A4 (see *Metabolism* above), with polymorphisms affecting clinical outcomes. For example, CYP3A4 polymorphisms influenced response in an observational clinical study of humans undergoing revascularization for critical limb ischemia being managed with transdermal buprenorphine (Blanco et al., 2016). Visual analog scale scores for subjects with a CYP3A4 allele variant were higher (i.e., less pain control) than those homozygous for the non-variant CYP3A4 allele (Blanco et al., 2016). In phase II buprenorphine metabolism, a SNP in UGT2B7 was shown to increase enzymatic activity and glucuronidation (Rouguieg et al., 2010). Buprenorphine-treated UGT2B7 variant-carrying subjects who had undergone thoracotomy exhibited decreased pain control at rest, decreased pain control with coughing, and increased severe pain scores (Sastre et al., 2015). This evidence supports the notion that in humans, phase I or phase II metabolic gain-of-function may diminish the response to buprenorphine.

In cats, there is some evidence of a variable response to opioids due to polymorphisms. Thermal thresholds and minimum alveolar concentration (MAC) suppression variability were examined in five groups of cats (Taylor et al., 2007). Three of the groups were from published thermal threshold or MAC suppression studies (Lascelles & Robertson, 2004; Pypendop et al., 2006; Robertson, 2006). Thermal thresholds were examined before and after treatment with buprenorphine (0.02 mg/kg), butorphanol (0.4 mg/kg), or morphine, and MAC suppression was tested following epidural buprenorphine (12.5 μg/kg) or morphine (100 μg/kg). Some cats did not exhibit an increased thermal threshold or decreased MAC following treatment with one or more opioids. Results were reproducible in some cats administered the same treatment more than once. This outcome supports the notion that some cats are 'non-responders' to various opioids and that alternative opioids should be used if the initially administered opioid is ineffective. It was hypothesized that these differences may be genetic, and a follow-up pilot study examined antinociceptive phenotypes in cats with confirmed polymorphisms (Slingsby et al., 2014). The five exons of the μ-opioid receptor gene were sequenced from 12 laboratory cats with historical thermal threshold data (Slingsby et al., 2012). Several SNPs and insertion/deletions identified divided cats into two haplotypes groups, one having different thermal threshold responses for fentanyl and butorphanol. No differences were observed for buprenorphine and methadone. Future studies should determine genetic markers for predicting opioid responsiveness. Until then, cats deemed as non-responsive to one opioid should be administered an alternative.

TABLE 10 Formulation differences in approved feline products

Proprietary name	Presentation	Preservative	When broached
Vetergesic™ (CEVA, UK and others)	1 ml clear glass snap ampules	None	Use immediately after opening
Vetergesic™ Multidose (CEVA, UK), national, informed consent	10 ml amber glass vials	Chlorocresol	Shelf life after first broaching the vial: 28 days[a]
Simbadol™ (Zoetis, USA)	10 ml amber glass vial	Ethanol, propylparaben, sodium acetate, methylparaben	Use within 56 days of first puncture
Bupaq™, (Richter Pharma, UK and others)	2 ml clear glass vials	None	24 h after opening if stored in refrigerator (2–8°C)
Buprelieve™ (Jurox, UK)	10 ml amber glass vial	Benzethonium chloride	28 days upon first opening[a]
Zorbium™ (Elanco, USA)	8 and 20 mg use-and-dispose applicator tubes	Butyl-hydroxy-anisole Butyl-hydroxy-toluene	Not applicable

[a]The beyond-use date for needle-punctured multiple-dose containers is 28 days, unless otherwise specified by the manufacturer on the label ("EMEA/CVMP/315/98").

Polymorphisms in the genes associated with buprenorphine metabolism and brain distribution in cats have not yet been described. Nevertheless, there is some indirect evidence of polymorphisms based on PK variability. Following IV administration of aqueous buprenorphine solution, the half-lives of buprenorphine in cats range from approximately 1–12 h (Doodnaught et al., 2017; Freise et al., 2022; Hedges, Pypendop, Shilo-Benjamini, et al., 2014; Steagall et al., 2013; Taylor et al., 2001). Moreover, there was variation in norbuprenorphine detection and concentration among cats, which may reflect individual animal differences in metabolic capability (Porters et al., 2015; Taylor et al., 2016). It is not clear what accounts for these differences as the cat homologs of CYP3A and UGT1A1 have not been characterized. However, given the presumed hepatic metabolism and excretion routes of buprenorphine in cats, gene polymorphisms or diminished organ function may impact its PK profile. In practice, this may not be of great concern given the safety margin of buprenorphine. There were no significant safety-related findings when the high-concentration buprenorphine solution was administered up to five times the label dose for 9 days (Sramek et al., 2015) or when TBS was administered at three times the label dose over 12 days (Clark, Linton, Freise, Reinemeyer, et al., 2022). Therefore, even with diminished drug metabolism and subsequent drug accumulation, adverse events are unlikely to occur in cats.

In general, there have been no reports of buprenorphine adverse effects in cats, which could be attributed to pharmacogenomic variability in opioid receptors (except opioid non-responders), metabolism, or brain distribution. However, as a greater understanding of pharmacogenomics in cats emerges, it remains possible that variable effects may be linked to genetic polymorphisms.

2.13.5 | Drug–Drug interactions

Although direct evidence of buprenorphine drug–drug interactions in cats is limited, some generalizations can be made based on presumed mechanisms. In humans, buprenorphine is highly bound to α-globulin and β-globulin, but not albumin. Therefore, drugs that are highly bound by albumin, such as nonsteroidal anti-inflammatory drugs, will not displace buprenorphine to increase its free fraction.

Unlike some other opioids, buprenorphine does not have a clinically relevant effect on the MAC of isoflurane in cats (Ilkiw et al., 2002). Morphine (1.0 mg/kg IV) and butorphanol (0.08 and 0.8 mg/kg IV) significantly reduce the MAC of isoflurane, which is considered clinically important. Although statistically significant, reductions in the MAC of isoflurane induced by morphine (0.1 mg/kg IV), buprenorphine (0.005 and 0.05 mg/kg IV), and U50488H (0.02 and 0.2 mg/kg [a selective κ-opioid receptor agonist]) were not considered clinically relevant as they fell within the error of the measurement technique employed. When morphine (100 μg/kg) or buprenorphine (12.5 μg/kg) were administered epidurally, there was no effect on the MAC of isoflurane (Pypendop et al., 2006). Therefore, morphine or butorphanol decrease the need for potent inhalant anesthetics in cats, which is not the case with buprenorphine.

While comprehensive characterization of feline cytochromes and UGTs is currently lacking (see *Metabolism* above), there is some indirect evidence CYP3A-mediated drug–drug interactions in cats. Ketoconazole, a potent inhibitor of CYP3A4 in humans, was shown to interact with cyclosporine presumably via its effects on the feline CYP3A ortholog and/or an interaction with the p-glycoprotein (McAnulty & Lensmeyer, 1999). Itraconazole is another CYP3A4 inhibitor (Sakaeda et al., 2005), that should be given with caution when drugs metabolized by this enzyme are co-administered. Whether ketoconazole or itraconazole can influence the effects of buprenorphine in cats remains to be determined.

Predicting drug–drug interactions that seem to involve CYP3A is complicated by the fact that many CYP3A substrates are also substrates of p-glycoprotein (Trepanier, 2006). Buprenorphine is not a p-glycoprotein substrate and thus p-glycoprotein-mediated drug–drug interactions are not expected (Hassan et al., 2009). However, norbuprenorphine is a p-glycoprotein substrate and therefore distribution

into or exclusion from the brain is regulated by p-glycoprotein, as demonstrated in p-glycoprotein knockout mice without the multiple drug resistant gene (Brown et al., 2012). Drug–drug interactions related to norbuprenorphine and other p-glycoprotein substrates have not been elucidated in cats. Known p-glycoprotein substrates include ketoconazole, itraconazole, erythromycin, cortisol, digoxin, diltiazem, cyclosporine, and ondansetron (Mealey, 2004). Given the paucity of data on cat p-glycoprotein, precautionary drug–drug recommendations with buprenorphine are currently lacking.

2.14 | Scheduling

The 1971 Convention of Psychotropic Substances, a United Nations treaty, introduced control provisions for narcotics, including buprenorphine. These provisions aimed to prevent diversion and abuse by limiting the prescription and clinical use of controlled substances to licensed parties. Global jurisdictions introduced systems and agencies to comply with these provisions. For example, United Kingdom's Home Office considers buprenorphine a Class C-controlled drug. In Australia, buprenorphine is a Schedule 8 (S8) controlled drug. In USA, buprenorphine was originally classified as a Schedule V drug when approved in 1982. In 2002, a review of USA and international data by the Department of Health and Human Services recommended that the Drug Enforcement Agency classify buprenorphine as Schedule III. Currently, all buprenorphine-containing products, including those used in veterinary medicine, are classified as Schedule III.

There are several control mechanisms that prevent the diversion and abuse of veterinary formulations. The US-approved high-concentration solution and TBS are labeled for in-hospital use only (Table 2). Moreover, under federal, state, and local law (where appropriate), scheduled drugs must be maintained in locked storage areas with use documented in a log subject to inspection. Extra-label use of human-approved buprenorphine formulations or compounded formulations used in veterinary medicine are subject to the same control. There are some practices of pre-loading syringes with compounded buprenorphine that are dispensed to owners for repeated OTM administrations at home (Steagall et al., 2014) although this does not alleviate the legal responsibility required for controlled substances.

2.15 | Formulation differences

The buprenorphine molecule is subject to oxidation that impacts the stability and shelf life of commercial formulations. At ambient temperatures, buprenorphine is oxidized to as many as 14 impurities, the major being 10-keto-buprenorphine (Vanderbist et al., 2008). To overcome this stability problem, the first injectable formulation approved for use in humans (Table 1) was manufactured in sealed 1 ml ampules in nitrogen gas (i.e., without oxygen). Although stable at room temperature, the instructions for clinical use were to snap the ampule open and use immediately.

Formulation differences for feline-approved products are summarized in Table 10. The first injectable buprenorphine formulation approved for use in veterinary medicine in the UK in 1995 was manufactured in sealed 1 ml, single-use ampules in nitrogen gas. The product was stable at room temperature and had to be used immediately upon opening the ampule. This formulation was developed from the human-approved injectable product and introduced certain logistical difficulties when used in companion animals. The approved dose was 0.6 ml per 10 kg of body weight, with most cats receiving less than an ampule, and the remainder had to be accounted for and disposed of.

In 2009, preservative-free ampules were reformulated and introduced as 10 ml multi-dose bottles. The new formulation contained buprenorphine (0.3 mg/ml) in a 5% glucose solution (pH 3.5–6.5) and 0.135% chlorocresol as a preservative (Vetergesic Multidose Injection; Alstoe [now Ceva]). Once broached, the product must be used within 28 days as per regulations ("EMEA/CVMP/315/98 1999"). This formulation obviated the need for disposal of unused drug remaining in opened, single-use ampules. Following its introduction into the clinic, there were anecdotal reports suggesting that the preserved formulation was more painful to administer compared with the preservative-free formulation. In addition to injection site pain, there were observations of profuse salivation and vomiting, which led to the examination of compounded OTM formulations to eliminate the need for injection (Bortolami et al., 2012).

The stability of a compounded buprenorphine solution intended for OTM administration has been examined (Gulledge et al., 2018). A 0.3 mg/ml buprenorphine syrup solution was prepared from commercially available 2 mg buprenorphine hydrochloride tablets approved by the FDA for sublingual use in humans. Batches were stored in plastic vials at room temperature (22–24°C) with light exposure or refrigerated at 4°C away from light. Crystals formed around the rim of a bottle stored at room temperature but not at refrigeration. However, buprenorphine concentrations were stable over 21 days in both storage conditions. The extent of absorption for the compounded formulation was significantly lower than OTM administration of the commercially available buprenorphine solution (0.3 mg/ml).

In another study, the systemic exposures of two suppository formulations were compared following rectal administration (Schroers et al., 2019). These were compounded from human-approved sublingual tablets and gel from the human-approved injectable solution (0.3 mg/ml) at 0.02 and 0.1 mg/kg doses, respectively. Systemic exposure was deemed submaximal, and clinical use was not recommended.

The stability of pre-loaded buprenorphine syringes dispensed to owners for repeated at-home OTM administrations has not been studied. It remains possible that high-temperature storage (e.g., car or countertop), even temporarily, could result in buprenorphine oxidation. Also, the adsorption of buprenorphine onto plastic or rubber syringe components has not been examined. It remains possible that even when stored under refrigeration, oxidation or adsorption to

syringe components could be associated with buprenorphine stored in syringes.

The approved high-concentration buprenorphine solution ('Simbadol; Zoetis') is formulated in 10 ml amber glass, multi-dose vials. Each vial contains buprenorphine (0.24 mg/ml), acetic acid, ethanol, glucose, propylparaben, sodium acetate, methylparaben, and water. Once the vial has been broached, it must be used within 56 days of first puncture.

In 2021, a multidose buprenorphine solution (Buprelieve, Jurox, UK) that contains the preservative benzethonium chloride (0.1 mg/ml) was introduced. This change was made to reduce pain on injection when compared to buprenorphine multidose formulations that are preserved with chlorocresol 1.35 mg/ml. This formulation comes in a 10 ml amber vial, and once broached it must be used within 28 days consistent with regulations.

In 2022, TBS was approved for use in cats in USA. It is manufactured as a non-aqueous solution in two strengths (8 and 20 mg) to be stored at room temperature. The contents of one use-and-dispose tube (Figure 13) are intended to treat one cat when applied topically to the unclipped dorsal cervical area. In laboratory and clinical studies, TBS was well-tolerated at the application site (Clark et al., 2022a, 2022b; Clark, Linton, Freise, Reinemeyer, et al., 2022; Freise et al., 2022).

3 | CONCLUSION

The historical search for an opiate analog that retains effective analgesic qualities without detrimental side effects led to the synthesis of buprenorphine. Its analgesic efficacy and favorable safety profile resulted in the approval of formulations for human use. Advances in receptor theory and molecular cloning of opioid receptors have led to a greater understanding of the complex buprenorphine pharmacology. Its introduction into feline medicine has resulted in the approval of low- and high-concentration injectable solutions, and, most recently, a long-acting transdermal formulation. Several investigational and compounded formulations have also been evaluated. There are contrasting differentiable features that include pharmacokinetics, onsets- and durations-of-action, routes of administration, and formulation constituents. The available buprenorphine formulations allow clinicians to select a formulation based on the anticipated duration of pain associated with various surgical procedures, and to provide interventions as needed.

ACKNOWLEDGMENTS

This study was funded by Elanco Animal Health and Nexcyon Pharmaceuticals, Inc.

ANIMAL WELFARE AND ETHICS STATEMENT

Not applicable. [Correction added on 26 August 2022, after first online publication: The Animal Welfare and Ethics Statement was included in this current version.]

CONFLICT OF INTEREST

At the time the paper was written, the author was a paid employee of Nexcyon Pharmaceuticals, Inc. and a paid consultant of Elanco Animal Health.

AUTHOR CONTRIBUTION

Author contributed to all of the manuscript.

REFERENCES

Abbo, L. A., Ko, J. C., Maxwell, L. K., Galinsky, R. E., Moody, D. E., Johnson, B. M., & Fang, W. B. (2008). Pharmacokinetics of buprenorphine following intravenous and oral transmucosal administration in dogs. *Veterinary Therapeutics*, *9*, 83–93.

Akkerdaas, L. C., Mioch, P., Sap, R., & Hellebrekers, L. J. (2001). Cardiopulmonary effects of three different anaesthesia protocols in cats. *Veterinary Quarterly*, *23*, 182–186.

Anchersen, K., Clausen, T., Gossop, M., Hansteen, V., & Waal, H. (2009). Prevalence and clinical relevance of corrected QT interval prolongation during methadone and buprenorphine treatment: A mortality assessment study. *Addiction*, *104*, 993–999.

Andaluz, A., Moll, X., Abellan, R., Ventura, R., Carbo, M., Fresno, L., & Garcia, F. (2009). Pharmacokinetics of buprenorphine after intravenous administration of clinical doses to dogs. *The Veterinary Journal*, *181*, 299–304.

Andaluz, A., Moll, X., Ventura, R., Abellan, R., Fresno, L., & Garcia, F. (2009). Plasma buprenorphine concentrations after the application of a 70 microg/h transdermal patch in dogs. Preliminary report. *Journal of Veterinary Pharmacology and Therapeutics*, *32*, 503–505.

Andrews, C. M., Krantz, M. J., Wedam, E. F., Marcuson, M. J., Capacchione, J. F., & Haigney, M. C. (2009). Methadone-induced mortality in the treatment of chronic pain: Role of QT prolongation. *Cardiology Journal*, *16*, 210–217.

Bauquier, S. H. (2012). Hypotension and pruritus induced by neuraxial anaesthesia in a cat. *Australian Veterinary Journal*, *90*, 402–403.

Bell, J. A., & Shannon, H. E. (1988). Partial agonists of the morphine type: Facilitative effects on electrophysiologically recorded C-fiber reflexes in the cat. *Neuropharmacology*, *27*, 649–652.

Bellini, L., Mollo, A., Contiero, B., & Busetto, R. (2017). Intraoperative end-tidal concentration of isoflurane in cats undergoing ovariectomy that received tramadol, buprenorphine or a combination of both. *Journal of Feline Medicine and Surgery*, *19*, 110–116.

Berti, J. J., & Lipsky, J. J. (1995). Transcutaneous drug delivery: A practical review. *Mayo Clin Proc*, *70*, 581–586.

Bhalla, R. J., Trimble, T. A., Leece, E. A., & Vettorato, E. (2018). Comparison of intramuscular butorphanol and buprenorphine combined with dexmedetomidine for sedation in cats. *Journal of Feline Medicine and Surgery*, *20*, 325–331.

Blanco, F., Muriel, C., Labrador, J., Gonzalez-Porras, J. R., Gonzalez-Sarmiento, R., & Lozano, F. S. (2016). Influence of UGT2B7, CYP3A4, and OPRM1 gene polymorphisms on transdermal buprenorphine pain control in patients with critical lower limb ischemia awaiting revascularization. *Pain Practice*, *16*, 842–849.

Boas, R. A., & Villiger, J. W. (1985). Clinical actions of fentanyl and buprenorphine. The significance of receptor binding. *British Journal of Anaesthesia*, *57*, 192–196.

Borrell, J., & Borrell, S. (1975). Chronic administration of morphine in cats: Effects on adrenal and urinary catecholamines. *European Journal of Pharmacology*, *32*, 337–343.

Bortolami, E., & Love, E. J. (2015). Practical use of opioids in cats: A state-of-the-art, evidence-based review. *Journal of Feline Medicine and Surgery*, *17*, 283–311.

Bortolami, E., Murrell, J. C., & Slingsby, L. S. (2013). Methadone in combination with acepromazine as premedication prior to neutering in the cat. *Veterinary Anaesthesia and Analgesia*, *40*, 181–193.

Bortolami, E., Slingsby, L., & Love, E. J. (2012). Comparison of two formulations of buprenorphine in cats administered by the oral transmucosal route. *Journal of Feline Medicine and Surgery*, *14*, 534–539.

Brewster, D., Humphrey, M. J., & McLeavy, M. A. (1981a). Biliary excretion, metabolism and enterohepatic circulation of buprenorphine. *Xenobiotica*, *11*, 189–196.

Brewster, D., Humphrey, M. J., & McLeavy, M. A. (1981b). The systemic bioavailability of buprenorphine by various routes of administration. *Journal of Pharmacy and Pharmacology*, *33*, 500–506.

Brown, S. M., Campbell, S. D., Crafford, A., Regina, K. J., Holtzman, M. J., & Kharasch, E. D. (2012). P-glycoprotein is a major determinant of norbuprenorphine brain exposure and antinociception. *Journal of Pharmacology and Experimental Therapeutics*, *343*, 53–61.

Bunzow, J. R., Saez, C., Mortrud, M., Bouvier, C., Williams, J. T., Low, M., & Grandy, D. K. (1994). Molecular cloning and tissue distribution of a putative member of the rat opioid receptor gene family that is not a mu, delta or kappa opioid receptor type. *FEBS Letter*, *347*, 284–288.

Burgess, J. W., & Villablanca, J. R. (2007). Ontogenesis of morphine-induced behavior in the cat. *Brain Research*, *1134*, 53–61.

van Beusekom, C. D., Schipper, L., & Fink-Gremmels, J. (2010). Cytochrome P450-mediated hepatic metabolism of new fluorescent substrates in cats and dogs. *Journal of Veterinary Pharmacology and Therapeutics*, *33*, 519–527.

Campbell, W.A. (1971). "*The analytical chemist in the nineteenth century English social history*." [Durham E-Theses Online, Durham University].

Cannarozzo, C. J., P. Kirch, L. Campoy, R. D. Gleed, A. M. Lorenzutti, and M. Martin-Flores. 2021. Retrospective investigation of an association between high-dose buprenorphine and perpetuation of postanesthesia hyperthermia in cats following ovariohysterectomy. *Journal of Feline Medicine and Surgery*, *23*(8), 777–782.

Catbagan, D. L., Quimby, J. M., Mama, K. R., Rychel, J. K., & Mich, P. M. (2011). Comparison of the efficacy and adverse effects of sustained-release buprenorphine hydrochloride following subcutaneous administration and buprenorphine hydrochloride following oral transmucosal administration in cats undergoing ovariohysterectomy. *American Journal of Veterinary Research*, *72*, 461–466.

'Ceva Animal Health'. Vetergesic. https://www.noahcompendium.co.uk/?id=-448845

Chang, Y., & Moody, D. E. (2009). Glucuronidation of buprenorphine and norbuprenorphine by human liver microsomes and UDP-glucuronosyltransferases. *Drug Metabolism Letters*, *3*, 101–107.

Chen, Y., Fan, Y., Liu, J., Mestek, A., Tian, M., Kozak, C. A., & Yu, L. (1994). Molecular cloning, tissue distribution and chromosomal localization of a novel member of the opioid receptor gene family. *FEBS Letters*, *347*, 279–283.

Chen, Y., Mestek, A., Liu, J., Hurley, J. A., & Yu, L. (1993). Molecular cloning and functional expression of a mu-opioid receptor from rat brain. *Molecular Pharmacology*, *44*, 8–12.

Chen, Y., Mestek, A., Liu, J., & Yu, L. (1993). Molecular cloning of a rat kappa opioid receptor reveals sequence similarities to the mu and delta opioid receptors. *Biochemical Journal*, *295*(Pt 3), 625–628.

Cherny, N., Ripamonti, C., Pereira, J., Davis, C., Fallon, M., McQuay, H., Mercadante, S., Pasternak, G., Ventafridda, V., & Network Expert Working Group of the European Association of Palliative Care. (2001). Strategies to manage the adverse effects of oral morphine: An evidence-based report. *Journal of Clinical Oncology*, *19*, 2542–2554.

Chou, R., Fanciullo, G. J., Fine, P. G., Adler, J. A., Ballantyne, J. C., Davies, P., Donovan, M. I., Fishbain, D. A., Foley, K. M., Fudin, J., Gilson, A. M., Kelter, A., Mauskop, A., O'Connor, P. G., Passik, S. D., Pasternak, G. W., Portenoy, R. K., Rich, B. A., Roberts, R. G., … Panel American Pain Society-American Academy of Pain Medicine Opioids Guidelines. (2009). Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *Journal of Pain*, *10*, 113–130.

Christoph, T., Kogel, B., Schiene, K., Meen, M., De Vry, J., & Friderichs, E. (2005). Broad analgesic profile of buprenorphine in rodent models of acute and chronic pain. *European Journal of Pharmacology*, *507*, 87–98.

Clark, J. A., Liu, L., Price, M., Hersh, B., Edelson, M., & Pasternak, G. W. (1989). Kappa opiate receptor multiplicity: Evidence for two U50,488-sensitive kappa 1 subtypes and a novel kappa 3 subtype. *Journal of Pharmacology and Experimental Therapeutics*, *251*, 461–468.

Clark, T. P., Linton, D. L., Freise, K. J., & Lin, T. (2022a). A multicentered masked placebo-controlled phase 2 clinical study of an extended duration transdermal buprenorphine solution for postoperative pain in cats. *Journal of Veterinary Pharmacology and Therapeutics*, *45*(Supplement 1), S40–S51. https://doi.org/10.1111.JVP13059

Clark, T. P., Linton, D. L., Freise, K. J., & Lin, T. (2022b). A multicentered masked placebo-controlled phase 3 clinical study of an extended duration transdermal buprenorphine solution for postoperative pain in cats. *Journal of Veterinary Pharmacology and Therapeutics*, *45*(Supplement 1), S52–S66. https://doi.org/10.1111.JVP13060

Clark, T. P., Linton, D. L., Freise, K. J., Reinemeyer, C., Newkirk, K., Aulbach, A., & Lin, T. (2022). Margin of safety of extended duration transdermal buprenorphine solution following multiple dose administrations to cats. *Journal of Veterinary Pharmacology and Therapeutics*, *45*(Supplement 1), S67–S84. https://doi.org/10.1111.JVP13051

Cone, E. J., Gorodetzky, C. W., Yousefnejad, D., Buchwald, W. F., & Johnson, R. E. (1984). The metabolism and excretion of buprenorphine in humans. *Drug Metabolism and Disposition*, *12*, 577–581.

Cook, D. A., & Beckman, T. J. (2006). Current concepts in validity and reliability for psychometric instruments: Theory and application. *American Journal of Medicine*, *119*(166), e7–e16.

Cools, A. R., & van Rossum, J. M. (1970). Caudal dopamine and stereotype behaviour of cats. *Archives Internationales de Pharmacodynamie et de Therapie*, *187*, 163–173.

Cowan, A. (2003). Buprenorphine: New pharmacological aspects. *International Journal of Clinical Practice Supplement*, (133), 3–8 discussion 23–4.

Cowan, A., Doxey, J. C., & Harry, E. J. (1977). The animal pharmacology of buprenorphine, an oripavine analgesic agent. *British Journal of Pharmacology*, *60*, 547–554.

Cowan, A., Lewis, J. W., & Macfarlane, I. R. (1977). Agonist and antagonist properties of buprenorphine, a new antinociceptive agent. *British Journal of Pharmacology*, *60*, 537–545.

Cowan, A., Lewis, J. W., Macfarlane, I. R., & Whittle, B. A. (1971). Analgesic and dependence studies with oripavine partial agonists. *British Journal of Pharmacology*, *43*, 461P–462P.

Crist, R. C., Clarke, T. K., Ang, A., Ambrose-Lanci, L. M., Lohoff, F. W., Saxon, A. J., Ling, W., Hillhouse, M. P., Bruce, R. D., Woody, G., & Berrettini, W. H. (2013). An intronic variant in OPRD1 predicts treatment outcome for opioid dependence in African-Americans. *Neuropsychopharmacology*, *38*, 2003–2010.

Crist, R. C., Phillips, K. A., Furnari, M. A., Moran, L. M., Doyle, G. A., McNicholas, L. F., Cornish, J. W., Kampman, K. M., Preston, K. L., & Berrettini, W. H. (2019). Replication of the pharmacogenetic effect of rs678849 on buprenorphine efficacy in African-Americans with opioid use disorder. *Pharmacogenomics Journal*, *19*, 260–268.

Cuer, J. C., Dapoigny, M., Ajmi, S., Larpent, J. L., Lunaud, B., Ferrier, C., & Bommelaer, G. (1989). Effects of buprenorphine on motor activity of the sphincter of Oddi in man. *European Journal of Clinical Pharmacology*, *36*, 203–204.

Dahan, A., Yassen, A., Romberg, R., Sarton, E., Teppema, L., Olofsen, E., & Danhof, M. (2006). Buprenorphine induces ceiling in respiratory depression but not in analgesia. *Br J Anaesth*, *96*, 627–632.

Dhasmana, K. M., Dixit, K. S., Jaju, B. P., & Gupta, M. L. (1972). Role of central dopaminergic receptors in manic response of cats to morphine. *Psychopharmacologia*, *24*, 380–383.

Ding, Z., & Raffa, R. B. (2009). Identification of an additional supraspinal component to the analgesic mechanism of action of buprenorphine. *British Journal of Pharmacology*, *157*, 831–843.

Dobbins, S., Brown, N. O., & Shofer, F. S. (2002). Comparison of the effects of buprenorphine, oxymorphone hydrochloride, and ketoprofen for postoperative analgesia after onychectomy or onychectomy and sterilization in cats. *Journal of the American Animal Hospital Association*, *38*, 507–514.

Doodnaught, G. M., Monteiro, B. P., Benito, J., Edge, D., Beaudry, F., Pelligand, L., & Steagall, P. (2017). Pharmacokinetic and pharmacodynamic modelling after subcutaneous, intravenous and buccal administration of a high-concentration formulation of buprenorphine in conscious cats. *PLoS One*, *12*, e0176443.

Duke-Novakovski, T., Clark, C. R., Ambros, B., Gilbert, P., & Steagall, P. V. (2011). Plasma concentrations of buprenorphine after epidural administration in conscious cats. *Research in Veterinary Science*, *90*, 480–483.

'Elanco'. (2002). Deramaxx. https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/717

'Elanco'. (2011). Onsior. https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/876

"EMEA/CVMP/315/98." (1999). The European Agency of the Evaluation of Medicinal Products.

Enomoto, M., Kigin, P. D., Bledsoe, D., Slone, R., Hash, J., Smith, C. E., & Lascelles, B. D. X. (2016). Pilot evaluation of a novel unilateral onychectomy model and efficacy of an extended release buprenorphine product. *BMC Veterinary Research*, *13*, 1–13.

Eppler, C. M., Hulmes, J. D., Wang, J. B., Johnson, B., Corbett, M., Luthin, D. R., Uhl, G. R., & Linden, J. (1993). Purification and partial amino acid sequence of a mu opioid receptor from rat brain. *Journal of Biological Chemistry*, *268*, 26447–26451.

Etches, R. C., Sandler, A. N., & Daley, M. D. (1989). Respiratory depression and spinal opioids. *Canadian Journal of Anaesthesia*, *36*, 165–185.

'Etodolac; Fort Dodge'. (1998). https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/2215

Evangelista, M. C., Doodnaught, G. M., Fantoni, D. T., & Steagall, P. V. M. (2017). Sciatic and femoral nerve blockade using bupivacaine alone, or in combination with dexmedetomidine or buprenorphine in cats. *Veterinary Record*, *180*, 592.

Evangelista, M. C., Steagall, P., Garofalo, N. A., Rodrigues, J. C., & Teixeira-Neto, F. (2016). Morphine-induced pruritus after epidural administration followed by treatment with naloxone in a cat. *Journal of Feline Medicine and Surgery Open Reports*, *2*, 2055116916634105.

Evans, C. J., Keith, D. E., Jr., Morrison, H., Magendzo, K., & Edwards, R. H. (1992). Cloning of a delta opioid receptor by functional expression. *Science*, *258*, 1952–1955.

Evans, H. C., & Easthope, S. E. (2003). Transdermal buprenorphine. *Drugs*, *63*, 1999–2010 discussion 11–2.

Faden, A. I., & Jacobs, T. P. (1985). Opiate antagonist WIN44,441–3 stereospecifically improves neurologic recovery after ischemic spinal injury. *Neurology*, *35*, 1311–1315.

Feline Mu-type opioid receptor. (2022). https://www.uniprot.org/uniprot/M3W3Y1

Ferreira, T. H., Rezende, M. L., Mama, K. R., Hudachek, S. F., & Aguiar, A. J. (2011). Plasma concentrations and behavioral, antinociceptive, and physiologic effects of methadone after intravenous and oral transmucosal administration in cats. *American Journal of Veterinary Research*, *72*, 764–771.

Fertziger, A. P., Stein, E. A., & Lynch, J. J. (1974). Suppression of morphine-induced mania in cats. *Psychopharmacologia*, *36*, 185–187.

Flamm, E. S., Young, W., Collins, W. F., Piepmeier, J., Clifton, G. L., & Fischer, B. (1985). A phase I trial of naloxone treatment in acute spinal cord injury. *Journal of Neurosurgery*, *63*, 390–397.

Fredriksson, R., Lagerstrom, M. C., Lundin, L. G., & Schioth, H. B. (2003). The G-protein-coupled receptors in the human genome form five main families. Phylogenetic analysis, paralogon groups, and fingerprints. *Molecular Pharmacology*, *63*, 1256–1272.

Freise, K. J., Lin, T. L., Fan, T. M., Recta, V., & Clark, T. P. (2013). Evidence-based medicine: The design and interpretation of noninferiority clinical trials in veterinary medicine. *Journal of Veterinary Internal Medicine*, *27*, 1305–1317.

Freise, K. J., Reinemeyer, C., Warren, K., Lin, T., & Clark, T. P. (2022). Single dose pharmacokinetics and bioavailability of a novel extended duration transdermal buprenorphine solution in cats. *Journal of Veterinary Pharmacology and Therapeutics*, *45*(Supplement 1), S30–S41. https://doi.org/10.1111.JVP13044

Fukuda, K., Kato, S., Mori, K., Nishi, M., Takeshima, H., Iwabe, N., Miyata, T., Houtani, T., & Sugimoto, T. (1994). cDNA cloning and regional distribution of a novel member of the opioid receptor family. *FEBS Letter*, *343*, 42–46.

Gassel, A. D., Tobias, K. M., Egger, C. M., & Rohrbach, B. W. (2005). Comparison of oral and subcutaneous administration of buprenorphine and meloxicam for preemptive analgesia in cats undergoing ovariohysterectomy. *Journal of the American Veterinary Medical Association*, *227*, 1937–1944.

Gellasch, K. L., Kruse-Elliott, K. T., Osmond, C. S., Shih, A. N., & Bjorling, D. E. (2002). Comparison of transdermal administration of fentanyl versus intramuscular administration of butorphanol for analgesia after onychectomy in cats. *Journal of the American Veterinary Medical Association*, *220*, 1020–1024.

Gerra, G., Somaini, L., Leonardi, C., Cortese, E., Maremmani, I., Manfredini, M., & Donnini, C. (2014). Association between gene variants and response to buprenorphine maintenance treatment. *Psychiatry Research*, *215*, 202–207.

Giordano, T., Steagall, P. V., Ferreira, T. H., Minto, B. W., de Sa Lorena, S. E., Brondani, J., & Luna, S. P. (2010). Postoperative analgesic effects of intravenous, intramuscular, subcutaneous or oral transmucosal buprenorphine administered to cats undergoing ovariohysterectomy. *Veterinary Anaesthesia and Analgesia*, *37*, 357–366.

Goldman, D., Oroszi, G., & Ducci, F. (2005). The genetics of addictions: Uncovering the genes. *Nature Reviews Genetics*, *6*, 521–532.

Goldstein, A., Lowney, L. I., & Pal, B. K. (1971). Stereospecific and nonspecific interactions of the morphine congener levorphanol in subcellular fractions of mouse brain. *Proceedings of the National Academy of Sciences of the United States of America*, *68*, 1742–1747.

Graybiel, A. M., Brecha, N., & Karten, H. J. (1984). Cluster-and-sheet pattern of enkephalin-like immunoreactivity in the superior colliculus of the cat. *Neuroscience*, *12*, 191–214.

Graybiel, A. M., & Chesselet, M. F. (1984). Compartmental distribution of striatal cell bodies expressing [met]enkephalin-like immunoreactivity. *Proceedings of the National Academy of Sciences of the United States of America*, *81*, 7980–7984.

Green, M. D., King, C. D., Mojarrabi, B., Mackenzie, P. I., & Tephly, T. R. (1998). Glucuronidation of amines and other xenobiotics catalyzed by expressed human UDP-glucuronosyltransferase 1A3. *Drug Metabolism and Disposition*, *26*, 507–512.

Grinnell, S. G., Ansonoff, M., Marrone, G. F., Lu, Z., Narayan, A., Xu, J., Rossi, G., Majumdar, S., Pan, Y. X., Bassoni, D. L., Pintar, J., & Pasternak, G. W. (2016). Mediation of buprenorphine analgesia by a combination of traditional and truncated mu opioid receptor splice variants. *Synapse*, *70*, 395–407.

Grint, N. J., Burford, J., & Dugdale, A. H. (2009). Investigating medetomidine-buprenorphine as preanaesthetic medication in cats. *Journal of Small Animal Practice*, *50*, 73–81.

Gulledge, B. M., Messenger, K. M., Cornell, K. K., Lindell, H., & Schmiedt, C. W. (2018). Pharmacokinetic comparison of two buprenorphine formulations after buccal administration in healthy male cats. *Journal of Feline Medicine and Surgery*, *20*, 312–318.

Hansen, B. D. (1994). Analgesic therapy. *Compendium on Continuing Education for the Practising Veterinarian*, *16*, 868–875.

Hansen, J. T., Brokaw, J., Christie, D., & Karasek, M. (1982). Localization of enkephalin-like immunoreactivity in the cat carotid and aortic body chemoreceptors. *Anatomical Record*, *203*, 405–410.

Harcus, A. H., Ward, A. E., & Smith, D. W. (1980). Buprenorphine in post-operative pain: Results in 7500 patients. *Anaesthesia*, *35*, 382–386.

Hassan, H. E., Myers, A. L., Coop, A., & Eddington, N. D. (2009). Differential involvement of P-glycoprotein (ABCB1) in permeability, tissue distribution, and antinociceptive activity of methadone, buprenorphine, and diprenorphine: In vitro and in vivo evaluation. *Journal of Pharmaceutical Sciences*, *98*, 4928–4940.

Hedges, A. R., Pypendop, B. H., Shilo, Y., Stanley, S. D., & Ilkiw, J. E. (2014). Impact of the blood sampling site on time-concentration drug profiles following intravenous or buccal drug administration. *Journal of Veterinary Pharmacology and Therapeutics*, *37*, 145–150.

Hedges, A. R., Pypendop, B. H., Shilo-Benjamini, Y., Stanley, S. D., & Ilkiw, J. E. (2014). Pharmacokinetics of buprenorphine following intravenous and buccal administration in cats, and effects on thermal threshold. *Journal of Veterinary Pharmacology and Therapeutics*, *37*, 252–259.

Heel, R. C., Brogden, R. N., Speight, T. M., & Avery, G. S. (1979). Buprenorphine: A review of its pharmacological properties and therapeutic efficacy. *Drugs*, *17*, 81–110.

Hillier, L.W., W. Warren, S. Obrien, and R.K. Wilson. (2011). "Sequence assembly of the *Felis catus* genome version 6.2." EMBL/GenBank/DDBJ databases.

Homberg, J. R., Mul, J. D., de Wit, E., & Cuppen, E. (2009). Complete knockout of the nociceptin/orphanin FQ receptor in the rat does not induce compensatory changes in mu, delta and kappa opioid receptors. *Neuroscience*, *163*, 308–315.

Huang, P., Kehner, G. B., Cowan, A., & Liu-Chen, L. Y. (2001). Comparison of pharmacological activities of buprenorphine and norbuprenorphine: Norbuprenorphine is a potent opioid agonist. *Journal of Pharmacology and Experimental Therapeutics*, *297*, 688–695.

Huang, W., Moody, D. E., & McCance-Katz, E. F. (2006). The in vivo glucuronidation of buprenorphine and norbuprenorphine determined by liquid chromatography-electrospray ionization-tandem mass spectrometry. *Therapeutic Drug Monitoring*, *28*, 245–251.

Huidobro, F., & Lewin, J. (1969). Tolerance and physical dependence to morphine in the cat. *Acta physiologica Latino Americana*, *19*, 345–350.

Ilkiw, J. E., Pascoe, P. J., & Tripp, L. D. (2002). Effects of morphine, butorphanol, buprenorphine, and U50488H on the minimum alveolar concentration of isoflurane in cats. *American Journal of Veterinary Research*, *63*, 1198–1202.

Indivior UK Limited. (1980). Temgesic sublingual tablets. https://www.medicines.org.uk/emc/product/1142/smpc

Inturrisi, C. E. (2002). Clinical pharmacology of opioids for pain. *The Clinical Journal of Pain*, *18*, S3–S13.

Iribarne, C., Picart, D., Dreano, Y., Bail, J. P., & Berthou, F. (1997). Involvement of cytochrome P450 3A4 in N-dealkylation of buprenorphine in human liver microsomes. *Life Science*, *60*, 1953–1964.

Jiang, Q., Takemori, A. E., Sultana, M., Portoghese, P. S., Bowen, W. D., Mosberg, H. I., & Porreca, F. (1991). 'Differential antagonism of opioid delta antinociception by [D-Ala2,Leu5,Cys6]enkephalin and naltrindole 5'-isothiocyanate: Evidence for delta receptor subtypes. *Journal of Pharmacology and Experimental Therapeutics*, *257*, 1069–1075.

Johard, E., Tidholm, A., Ljungvall, I., Haggstrom, J., & Hoglund, K. (2018). Effects of sedation with dexmedetomidine and buprenorphine on echocardiographic variables, blood pressure and heart rate in healthy cats. *Journal of Feline Medicine and Surgery*, *20*, 554–562.

Johnson, J. A., Robertson, S. A., & Pypendop, B. H. (2007). Antinociceptive effects of butorphanol, buprenorphine, or both, administered intramuscularly in cats. *American Journal of Veterinary Research*, *68*, 699–703.

Johnson, R. E., Fudala, P. J., & Payne, R. (2005). Buprenorphine: Considerations for pain management. *Journal of Pain and Symptom Management*, *29*, 297–326.

Johnson, R. J., Kerr, C. L., Enouri, S. S., Modi, P., Lascelles, B. D. X., & Del Castillo, J. R. E. (2017). Pharmacokinetics of liposomal encapsulated buprenorphine suspension following subcutaneous administration to cats. *Journal of Veterinary Pharmacology and Therapeutics*, *40*, 256–269.

Kakko, J., von Wachenfeldt, J., Svanborg, K. D., Lidstrom, J., Barr, C. S., & Heilig, M. (2008). Mood and neuroendocrine response to a chemical stressor, metyrapone, in buprenorphine-maintained heroin dependence. *Biological Psychiatry*, *63*, 172–177.

Kamei, J., Saitoh, A., Suzuki, T., Misawa, M., Nagase, H., & Kasuya, Y. (1995). Buprenorphine exerts its antinociceptive activity via mu 1-opioid receptors. *Life Sciences*, *56*, PL285–PL290.

Kamei, J., Sodeyama, M., Tsuda, M., Suzuki, T., & Nagase, H. (1997). Antinociceptive effect of buprenorphine in mu1-opioid receptor deficient CXBK mice. *Life Sciences*, *60*, 333–337.

Kawamoto, H., Ozaki, S., Itoh, Y., Miyaji, M., Arai, S., Nakashima, H., Kato, T., Ohta, H., & Iwasawa, Y. (1999). Discovery of the first potent and selective small molecule opioid receptor-like (ORL1) antagonist: 1-[(3R,4R)-1-cyclooctylmethyl-3- hydroxymethyl-4-piperidyl]-3-ethyl-1, 3-dihydro-2H-benzimidazol-2-one (J-113397). *Journal of Medical Chemistry*, *42*, 5061–5063.

Keith, D., Maung, T., Anton, B., & Evans, C. J. (1994). Isolation of cDNAclones homologous to opioid receptors. *Regulatory Peptides*, *54*, 143–144.

Kieffer, B. L., Befort, K., Gaveriaux-Ruff, C., & Hirth, C. G. (1992). The delta-opioid receptor: Isolation of a cDNA by expression cloning and pharmacological characterization. *Proceedings of the National Academy of Sciences of the United States of America*, *89*, 12048–12052.

King, C. D., Green, M. D., Rios, G. R., Coffman, B. L., Owens, I. S., Bishop, W. P., & Tephly, T. R. (1996). The glucuronidation of exogenous and endogenous compounds by stably expressed rat and human UDP-glucuronosyltransferase 1.1. *Archives of Biochemistry and Biophysics*, *332*, 92–100.

King, S., Roberts, E. S., Roycroft, L. M., & King, J. N. (2012). Evaluation of oral robenacoxib for the treatment of postoperative pain and inflammation in cats: Results of a randomized clinical trial. *ISRN Veterinary Science*, *2012*, 794148.

Kirby, G. C., & McQueen, D. S. (1986). Characterization of opioid receptors in the cat carotid body involved in chemosensory depression in vivo. *British Journal of Pharmacology*, *88*, 889–898.

Kitzmiller, J. P., Barnett, C. J., Steiner, N. S., Stoicea, N., Kamar, N., Luzum, J. A., Mikulik, E., & Bergese, S. D. (2015). Buprenorphine: Revisiting the efficacy of transdermal delivery system. *Therapeutic Delivery*, *6*, 419–422.

Kobayashi, K., Yamamoto, T., Chiba, K., Tani, M., Shimada, N., Ishizaki, T., & Kuroiwa, Y. (1998). Human buprenorphine N-dealkylation is catalyzed by cytochrome P450 3A4. *Drug Metabolism and Disposition*, *26*, 818–821.

Kozaki, Y., Tadaki, E., & Kumazawa, T. (2000). Morphine inhibits resting respiration, but it attenuates reflexive respiratory suppression in anesthetized cat through kappa-receptor. *The Japanese Journal of Physiology*, *50*, 615–624.

Krantz, M. J., Martin, J., Stimmel, B., Mehta, D., & Haigney, M. C. (2009). QTc interval screening in methadone treatment. *Annals of Internal Medicine*, *150*, 387–395.

Kukanich, B., & Papich, M. G. (2009). Opioid analgesic drugs. In J. E. Riviere & M. G. Papich (Eds.), *Veterinary Pharmacology & Therapeutics*. Wiley-Blackwell.

Lascelles, B., Robertson, S. A., Taylor, P. M., & Hauptman, J. (2003). Comparison of the pharmacokinetics and thermal antinociceptive

pharmacodynamics of 20 mug kg(−1) buprenorphine administered sublingually or intravenously in cats. *Veterinary Anaesthesia and Analgesia*, *30*, 108.

Lascelles, B. D., & Robertson, S. A. (2004). Use of thermal threshold response to evaluate the antinociceptive effects of butorphanol in cats. *American Journal of Veterinary Research*, *65*, 1085–1089.

Levran, O., Londono, D., O'Hara, K., Nielsen, D. A., Peles, E., Rotrosen, J., Casadonte, P., Linzy, S., Randesi, M., Ott, J., Adelson, M., & Kreek, M. J. (2008). Genetic susceptibility to heroin addiction: A candidate gene association study. *Genes, Brain and Behavior*, *7*, 720–729.

Lewis, J. W. (1985). Buprenorphine. *Drug Alcohol Dependence*, *14*, 363–372.

Li, S., Zhu, J., Chen, C., Chen, Y. W., Deriel, J. K., Ashby, B., & Liu-Chen, L. Y. (1993). Molecular cloning and expression of a rat kappa opioid receptor. *Biochemical Journal*, *295*(Pt 3), 629–633.

Likar, R. (2006). Transdermal buprenorphine in the management of persistent pain - safety aspects. *Therapeutics and Clinical Risk Management*, *2*, 115–125.

Likar, R., Kayser, H., & Sittl, R. (2006). Long-term management of chronic pain with transdermal buprenorphine: A multicenter, open-label, follow-up study in patients from three short-term clinical trials. *Clinical Therapeutics*, *28*, 943–952.

Loewe, S. (1956). Influence of chlorpromazine, reserpine, dibenzyline and desoxycorticosterone upon morphine-induced feline mania. *Archives Internationales de Pharmacodynamie et de Therapie*, *108*, 453–456.

Lord, J. A., Waterfield, A. A., Hughes, J., & Kosterlitz, H. W. (1977). Endogenous opioid peptides: Multiple agonists and receptors. *Nature*, *267*, 495–499.

Lotsch, J., Skarke, C., Liefhold, J., & Geisslinger, G. (2004). Genetic predictors of the clinical response to opioid analgesics: Clinical utility and future perspectives. *Clinical Pharmacokinetics*, *43*, 983–1013.

Lundberg, J. M., Hokfelt, T., Fahrenkrug, J., Nilsson, G., & Terenius, L. (1979). Peptides in the cat carotid body (glomus caroticum): VIP-, enkephalin-, and substance P-like immunoreactivity. *Acta Physiologica Scandinavica*, *107*, 279–281.

Lutfy, K., & Cowan, A. (2004). Buprenorphine: A unique drug with complex pharmacology. *Current Neuropharmacology*, *2*, 395–402.

Lutfy, K., Eitan, S., Bryant, C. D., Yang, Y. C., Saliminejad, N., Walwyn, W., Kieffer, B. L., Takeshima, H., Carroll, F. I., Maidment, N. T., & Evans, C. J. (2003). Buprenorphine-induced antinociception is mediated by mu-opioid receptors and compromised by concomitant activation of opioid receptor-like receptors. *Journal of Neuroscience*, *23*, 10331–10337.

Mahdmina, A., Evans, A., Yates, D., & White, K. L. (2020). Comparison of the effects of buprenorphine and methadone in combination with medetomidine followed by intramuscular alfaxalone for anaesthesia of cats undergoing ovariohysterectomy. *Journal of Feline Medicine and Surgery*, *22*, 77–83.

Martin, W. R., Eades, C. G., Thompson, J. A., Huppler, R. E., & Gilbert, P. E. (1976). The effects of morphine- and nalorphine- like drugs in the nondependent and morphine-dependent chronic spinal dog. *Journal of Pharmacology and Experimental Therapeutics*, *197*, 517–532.

Mayer, P., Rochlitz, H., Rauch, E., Rommelspacher, H., Hasse, H. E., Schmidt, S., & Hollt, V. (1997). Association between a delta opioid receptor gene polymorphism and heroin dependence in man. *Neuroreport*, *8*, 2547–2550.

McAnulty, J. F., & Lensmeyer, G. L. (1999). The effects of ketoconazole on the pharmacokinetics of cyclosporine a in cats. *Veterinary Surgery*, *28*, 448–455.

McQueen, D. S., & Ribeiro, J. A. (1980). Inhibitory actions of methionine-enkephalin and morphine on the cat carotid chemoreceptors. *British Journal of Pharmacology*, *71*, 297–305.

Meaden, C. W., Mozeika, A., Asri, R., & Santos, C. D. (2021). A review of the existing literature on buprenorphine pharmacogenomics. *Pharmacogenomics Journal*, *21*, 128–139.

Mealey, K. L. (2004). Therapeutic implications of the MDR-1 gene. *Journal of Veterinary Pharmacology and Therapeutics*, *27*, 257–264.

Meng, F., Xie, G. X., Thompson, R. C., Mansour, A., Goldstein, A., Watson, S. J., & Akil, H. (1993). Cloning and pharmacological characterization of a rat kappa opioid receptor. *Proceedings of the National Academy of Sciences of the United States of America*, *90*, 9954–9958.

Meunier, J. C., Mollereau, C., Toll, L., Suaudeau, C., Moisand, C., Alvinerie, P., Butour, J. L., Guillemot, J. C., Ferrara, P., Monsarrat, B., Mazarguil, H., Vassart, G., Parmentier, M., & Costentin, J. (1995). Isolation and structure of the endogenous agonist of opioid receptor-like ORL1 receptor. *Nature*, *377*, 532–535.

Mizoguchi, H., Spaulding, A., Leitermann, R., Wu, H. E., Nagase, H., & Tseng, L. F. (2003). Buprenorphine blocks epsilon- and micro-opioid receptor-mediated antinociception in the mouse. *Journal of Pharmacology and Experimental Therapeutics*, *306*, 394–400.

Mollenhoff, A., Nolte, I., & Kramer, S. (2005). Anti-nociceptive efficacy of carprofen, levomethadone and buprenorphine for pain relief in cats following major orthopaedic surgery. *Journal of Veterinary Medicine. A, Physiology, Pathology, Clinical Medicine*, *52*, 186–198.

Mollereau, C., Parmentier, M., Mailleux, P., Butour, J. L., Moisand, C., Chalon, P., Caput, D., Vassart, G., & Meunier, J. C. (1994). ORL1, a novel member of the opioid receptor family. Cloning, functional expression and localization. *FEBS Letter*, *341*, 33–38.

Monti-Bloch, L., & Eyzaguirre, C. (1985). Effects of methionine-enkephalin and substance P on the chemosensory discharge of the cat carotid body. *Brain Research*, *338*, 297–307.

Moreno, K. L., Scallan, E. M., Monteiro, B. P., Steagall, P. V., & Simon, B. T. (2021). The thermal antinociceptive effects of a high-concentration formulation of buprenorphine alone or followed by hydromorphone in conscious cats. *Veterinary Anaesthesia and Analgesia*, *48*, 570–576.

Morton, C. R., & Hutchison, W. D. (1990). Release of sensory neuropeptides in the cat spinal cord during morphine withdrawal. *Progress in Clinical and Biological Research*, *328*, 507–510.

Moser, K. L., Hasiuk, M. M., Armstrong, T., Gunn, M., & Pang, D. S. (2020). A randomized clinical trial comparing butorphanol and buprenorphine within a multimodal analgesic protocol in cats undergoing orchiectomy. *Journal of Feline Medicine and Surgery*, *22*, 760–767.

Murrell, J. C., Robertson, S. A., Taylor, P. M., McCown, J. L., Bloomfield, M., & Sear, J. W. (2007). Use of a transdermal matrix patch of buprenorphine in cats: Preliminary pharmacokinetic and pharmacodynamic data. *Veterinary Record*, *160*, 578–583.

'Napp Pharmaceuticals'. Transtec. https://www.medicines.org.uk/emc/product/1611/smpc

Nasar, M. A., McLeavy, M. A., & Knox, J. (1986). An open study of sublingual buprenorphine in the treatment of chronic pain in the elderly. *Current Medical Research and Opinion*, *10*, 251–255.

Nishi, M., Takeshima, H., Mori, M., Nakagawara, K., & Takeuchi, T. (1994). Structure and chromosomal mapping of genes for the mouse kappa-opioid receptor and an opioid receptor homologue (MOR-C). *Biochemical and Biophysical Research Communications*, *205*, 1353–1357.

Nunamaker, E. A., Halliday, L. C., Moody, D. E., Fang, W. B., Lindeblad, M., & Fortman, J. D. (2013). Pharmacokinetics of 2 formulations of buprenorphine in macaques (*Macaca mulatta* and *Macaca fascicularis*). *Journal of the American Association for Laboratory Animal Science*, *52*, 48–56.

Olson, K. M., Duron, D. I., Womer, D., Fell, R., & Streicher, J. M. (2019). Comprehensive molecular pharmacology screening reveals potential new receptor interactions for clinically relevant opioids. *PLoS One*, *14*, e0217371.

Pan, L., Xu, J., Yu, R., Xu, M. M., Pan, Y. X., & Pasternak, G. W. (2005). Identification and characterization of six new alternatively spliced variants of the human mu opioid receptor gene, Oprm. *Neuroscience*, *133*, 209–220.

Pan, Y. X., Cheng, J., Xu, J., & Pasternak, G. W. (1994). Cloning, expression and classification of a kappa3-related opioid receptor using antisense oligodeoxynucleotides. *Regulatory Peptides*, *54*, 217–218.

Pan, Y. X., Cheng, J., Xu, J., Rossi, G., Jacobson, E., Ryan-Moro, J., Brooks, A. I., Dean, G. E., Standifer, K. M., & Pasternak, G. W. (1995). Cloning and functional characterization through antisense mapping of a kappa 3-related opioid receptor. *Molecular Pharmacology*, *47*, 1180–1188.

Pan, Y. X., & Pasternak, G. W. (2011). Molecular biology of mu opioid receptors. In G. W. Pasternak (Ed.), *The opiate receptors*. Humana Press.

Pasternak, G. W. (2001). The pharmacology of mu analgesics: From patients to genes. *Neuroscientist*, *7*, 220–231.

Pasternak, G. W., Childers, S. R., & Snyder, S. H. (1980). Opiate analgesia: Evidence for mediation by a subpopulation of opiate receptors. *Science*, *208*, 514–516.

Pasternak, G. W., & Pan, Y. X. (2013). Mu opioids and their receptors: Evolution of a concept. *Pharmacological Reviews*, *65*, 1257–1317.

Purdue Pharma LP. (2010). Butrans Transdermal System. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021306s015s019lbl.pdf.

Pasternak, G. W., & Snyder, S. H. (1975). Identification of novel high affinity opiate receptor binding in rat brain. *Nature*, *253*, 563–565.

Pattinson, K. T. (2008). Opioids and the control of respiration. *British Journal of Anaesthesia*, *100*, 747–758.

Pergolizzi, J., Aloisi, A. M., Dahan, A., Filitz, J., Langford, R., Likar, R., Mercadante, S., Morlion, B., Raffa, R. B., Sabatowski, R., Sacerdote, P., Torres, L. M., & Weinbroum, A. A. (2010). Current knowledge of buprenorphine and its unique pharmacological profile. *Pain Practice*, *10*, 428–450.

Pert, A., & Yaksh, T. (1974). Sites of morphine induced analgesia in the primate brain: Relation to pain pathways. *Brain Research*, *80*, 135–140.

Pert, C. B., Pasternak, G., & Snyder, S. H. (1973). Opiate agonists and antagonists discriminated by receptor binding in brain. *Science*, *182*, 1359–1361.

Picard, N., Cresteil, T., Djebli, N., & Marquet, P. (2005). In vitro metabolism study of buprenorphine: Evidence for new metabolic pathways. *Drug Metabolism and Disposition*, *33*, 689–695.

Pokorski, M., Grieb, P., & Wideman, J. (1981). Opiate system influences central respiratory chemosensors. *Brain Research*, *211*, 221–226.

Pokorski, M., & Lahiri, S. (1981). Effects of naloxone on carotid body chemoreception and ventilation in the cat. *Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology*, *51*, 1533–1538.

Polson, S., Taylor, P. M., & Yates, D. (2012). Analgesia after feline ovariohysterectomy under midazolam-medetomidine-ketamine anaesthesia with buprenorphine or butorphanol, and carprofen or meloxicam: A prospective, randomised clinical trial. *Journal of Feline Medicine and Surgery*, *14*, 553–559.

Pontius, J. U., Mullikin, J. C., Smith, D. R., Team Agencourt Sequencing, Lindblad-Toh, K., Gnerre, S., Clamp, M., Chang, J., Stephens, R., Neelam, B., Volfovsky, N., Schaffer, A. A., Agarwala, R., Narfstrom, K., Murphy, W. J., Giger, U., Roca, A. L., Antunes, A., Menotti-Raymond, M., … O'Brien, S. J. (2007). Initial sequence and comparative analysis of the cat genome. *Genome Research*, *17*, 1675–1689.

Porters, N., Bosmans, T., Debille, M., de Rooster, H., Duchateau, L., & Polis, I. (2014). Sedative and antinociceptive effects of dexmedetomidine and buprenorphine after oral transmucosal or intramuscular administration in cats. *Veterinary Anaesthesia and Analgesia*, *41*, 90–96.

Porters, N., de Rooster, H., Bosmans, T., Baert, K., Cherlet, M., Croubels, S., De Backer, P., & Polis, I. (2015). Pharmacokinetics of oral transmucosal and intramuscular dexmedetomidine combined with buprenorphine in cats. *Journal of Veterinary Pharmacology and Therapeutics*, *38*, 203–208.

Posner, L. P., Gleed, R. D., Erb, H. N., & Ludders, J. W. (2007). Postanesthetic hyperthermia in cats. *Veterinary Anaesthesia and Analgesia*, *34*, 40–47.

Posner, L. P., Pavuk, A. A., Rokshar, J. L., Carter, J. E., & Levine, J. F. (2010). Effects of opioids and anesthetic drugs on body temperature in cats. *Veterinary Anaesthesia and Analgesia*, *37*, 35–43.

Pypendop, B. H., Pascoe, P. J., & Ilkiw, J. E. (2006). Effects of epidural administration of morphine and buprenorphine on the minimum alveolar concentration of isoflurane in cats. *American Journal of Veterinary Research*, *67*, 1471–1475.

Pypendop, B. H., Siao, K. T., Pascoe, P. J., & Ilkiw, J. E. (2008). Effects of epidurally administered morphine or buprenorphine on the thermal threshold in cats. *American Journal of Veterinary Research*, *69*, 983–987.

Raffa, R. B., & Ding, Z. (2007). Examiniation of preclinical antinociception efficacy of buprenorphine and its designation as a full- or partial-agonist. *Acute Pain*, *9*, 145–152.

Raffa, R. B., Haidery, M., Huang, H. M., Kalladeen, K., Lockstein, D. E., Ono, H., Shope, M. J., Sowunmi, O. A., Tran, J. K., & Pergolizzi, J. V., Jr. (2014). The clinical analgesic efficacy of buprenorphine. *Journal of Clinical Pharmacy and Therapeutics*, *39*, 577–583.

Rausch-Derra, L., Huebner, M., Wofford, J., & Rhodes, L. (2016). A prospective, randomized, masked, placebo-controlled multisite clinical study of Grapiprant, an EP4 prostaglandin receptor antagonist (PRA), in dogs with osteoarthritis. *Journal of Veterinary Internal Medicine*, *30*, 756–763.

Reinscheid, R. K., Nothacker, H. P., Bourson, A., Ardati, A., Henningsen, R. A., Bunzow, J. R., Grandy, D. K., Langen, H., Monsma, F. J., Jr., & Civelli, O. (1995). Orphanin FQ: A neuropeptide that activates an opioidlike G protein-coupled receptor. *Science*, *270*, 792–794.

Rios, G. R., & Tephly, T. R. (2002). Inhibition and active sites of UDP-glucuronosyltransferases 2B7 and 1A1. *Drug Metabolism and Disposition*, *30*, 1364–1367.

Robertson, S. (2006). *Proc 9th WCVA* (pp. 41–46). *Santos*.

Robertson, S. A., Lascelles, B. D., Taylor, P. M., & Sear, J. W. (2005). PK-PD modeling of buprenorphine in cats: Intravenous and oral transmucosal administration. *Journal of Veterinary Pharmacology and Therapeutics*, *28*, 453–460.

Robertson, S. A., & Taylor, P. M. (2004). Pain management in cats--past, present and future. Part 2. Treatment of pain--clinical pharmacology. *Journal of Feline Medicine and Surgery*, *6*, 321–333.

Robertson, S. A., Taylor, P. M., Bloomfield, M., & Sear, J. W. (2001). Buprenorphine disposition after buccal administration in cats: Preliminary observations. *Veterinary Anaesthesia and Analgesia*, *28*, 206–207.

Robertson, S. A., Taylor, P. M., Dixon, M. J., Sear, J. W., Ruprah, M., & Waters, C. (2001). Disposition of buprenorphine, morphine and meperidine in the cat. *Veterinary Anaesthesia and Analgesia*, *28*, 101.

Robertson, S. A., Taylor, P. M., Lascelles, B. D., & Dixon, M. J. (2003). Changes in thermal threshold response in eight cats after administration of buprenorphine, butorphanol and morphine. *Veterinary Record*, *153*, 462–465.

Robertson, S. A., Taylor, P. M., & Sear, J. W. (2003). Systemic uptake of buprenorphine by cats after oral mucosal administration. *Veterinary Record*, *152*, 675–678.

Rothman, R. B., Bykov, V., de Costa, B. R., Jacobson, A. E., Rice, K. C., & Brady, L. S. (1990). Interaction of endogenous opioid peptides and other drugs with four kappa opioid binding sites in Guinea pig brain. *Peptides*, *11*, 311–331.

Rouguieg, K., Picard, N., Sauvage, F. L., Gaulier, J. M., & Marquet, P. (2010). Contribution of the different UDP-glucuronosyltransferase (UGT) isoforms to buprenorphine and norbuprenorphine metabolism and relationship with the main UGT polymorphisms in a bank of human liver microsomes. *Drug Metabolism and Disposition*, *38*, 40–45.

Sadee, W., Rosenbaum, J. S., & Herz, A. (1982). Buprenorphine: Differential interaction with opiate receptor subtypes in vivo. *Journal of Pharmacology and Experimental Therapeutics*, *223*, 157–162.

Sadhasivam, S., & Chidambaran, V. (2012). Pharmacogenomics of opioids and perioperative pain management. *Pharmacogenomics*, *13*, 1719–1740.

Sakaeda, T., Iwaki, K., Kakumoto, M., Nishikawa, M., Niwa, T., Jin, J. S., Nakamura, T., Nishiguchi, K., Okamura, N., & Okumura, K. (2005). Effect of micafungin on cytochrome P450 3A4 and multidrug resistance protein 1 activities, and its comparison with azole antifungal drugs. *Journal of Pharmacy and Pharmacology*, *57*, 759–764.

Santos, L. C., Ludders, J. W., Erb, H. N., Basher, K. L., Kirch, P., & Gleed, R. D. (2010). Sedative and cardiorespiratory effects of dexmedetomidine and buprenorphine administered to cats via oral transmucosal or intramuscular routes. *Veterinary Anaesthesia and Analgesia*, *37*, 417–424.

Sastre, J. A., Varela, G., Lopez, M., Muriel, C., & Gonzalez-Sarmiento, R. (2015). Influence of uridine diphosphate-glucuronyltransferase 2B7 (UGT2B7) variants on postoperative buprenorphine analgesia. *Pain Practise*, *15*, 22–30.

Schroers, M., Meyer-Lindenberg, A., Reese, S., Dobenecker, B., & Pieper, K. (2019). Pharmacokinetics of low-dose and high-dose buprenorphine in cats after rectal administration of different formulations. *Journal of Feline Medicine and Surgery*, *21*, 938–943.

Shah, M., Yates, D., Hunt, J., & Murrell, J. (2019). Comparison between methadone and buprenorphine within the QUAD protocol for perioperative analgesia in cats undergoing ovariohysterectomy. *Journal of Feline Medicine and Surgery*, *21*, 723–731.

Shook, J. E., Watkins, W. D., & Camporesi, E. M. (1990). Differential roles of opioid receptors in respiration, respiratory disease, and opiate-induced respiratory depression. *The American Review of Respiratory Disease*, *142*, 895–909.

Simon, E. J., Hiller, J. M., & Edelman, I. (1973). Stereospecific binding of the potent narcotic analgesic (3H) etorphine to rat-brain homogenate. *Proceedings of the National Academy of Sciences of the United States of America*, *70*, 1947–1949.

Skarda, R. T., & Tranquilli, W. J. (2007). Local and regional anesthetic and analgesic techniques: Cats. In W. J. Tranquilli, J. C. Thurmon, & K. A. Grimm (Eds.), *Lumb & Jones Veterinary Anesthesia and analgesia*. Blackwell.

Slingsby, L. S., Helps, C. R., Murrell, J. C., & Taylor, P. M. (2014). Is there a genetic basis for the variable response to opioids in cats? A pilot study. *Veterinary Anaesthesia and Analgesia*, *41*, A60.

Slingsby, L. S., Murrell, J. C., & Taylor, P. M. (2012). Buprenorphine in combination with naloxone at a ratio of 15:1 does not enhance antinociception from buprenorphine in healthy cats. *Veterinary Journal*, *192*, 523–524.

Slingsby, L. S., & Waterman-Pearson, A. E. (1998). Comparison of pethidine, buprenorphine and ketoprofen for postoperative analgesia after ovariohysterectomy in the cat. *Veterinary Record*, *143*, 185–189.

Sparkes, A. H., Papasouliotis, K., Viner, J., Cripps, P. J., & Gruffydd-Jones, T. J. (1996). Assessment of orocaecal transit time in cats by the breath hydrogen method: The effects of sedation and a comparison of definitions. *Research in Veterinary Science*, *60*, 243–246.

Sramek, M. K., Haas, M. C., Coleman, G. D., Atterson, P. R., & Hamlin, R. L. (2015). The safety of high-dose buprenorphine administered subcutaneously in cats. *Journal of Veterinary Pharmacology and Therapeutics*, *38*, 434–442.

Stanway, G. W., Taylor, P. M., & Brodbelt, D. C. (1996). A comparison of pre-operative morphine and buprenorphine in cats. *Journal of Veterinary Anaesthesia*, *23*, 78.

Stanway, G. W., Taylor, P. M., & Brodbelt, D. C. (2002). A preliminary investigation comparing pre-operative morphine and buprenorphine for postoperative analgesia and sedation in cats. *Veterinary Anaesthesia and Analgesia*, *29*, 29–35.

Staritz, M., Poralla, T., Manns, M., & Buschenfelde, K. H. M. Z. (1986). Effect of modern analgesic drugs (tramadol, pentazocine, and buprenorphine) on the bile duct sphincter in man. *Gut*, *27*, 567–569.

Stathopoulou, T. R., Kouki, M., Pypendop, B. H., Johnston, A., Papadimitriou, S., & Pelligand, L. (2018). Evaluation of analgesic effect and absorption of buprenorphine after buccal administration in cats with oral disease. *Journal of Feline Medicine and Surgery*, *20*, 704–710.

Steagall, P. V., Benito, J., Monteiro, B. P., Doodnaught, G. M., Beauchamp, G., & Evangelista, M. C. (2018). Analgesic effects of gabapentin and buprenorphine in cats undergoing ovariohysterectomy using two pain-scoring systems: A randomized clinical trial. *Journal of Feline Medicine and Surgery*, *20*, 741–748.

Steagall, P. V., Carnicelli, P., Taylor, P. M., Luna, S. P., Dixon, M., & Ferreira, T. H. (2006). Effects of subcutaneous methadone, morphine, buprenorphine or saline on thermal and pressure thresholds in cats. *Journal of Veterinary Pharmacology and Therapeutics*, *29*, 531–537.

Steagall, P. V., Millette, V., Mantovani, F. B., Gilbert, P., Luna, S. P., & Duke-Novakovski, T. (2009). Antinociceptive effects of epidural buprenorphine or medetomidine, or the combination, in conscious cats. *Journal of Veterinary Pharmacology and Therapeutics*, *32*, 477–484.

Steagall, P. V., Monteiro-Steagall, B. P., & Taylor, P. M. (2014). A review of the studies using buprenorphine in cats. *Journal of Veterinary Internal Medicine*, *28*, 762–770.

Steagall, P. V., Pelligand, L., Giordano, T., Auberger, C., Sear, J. W., Luna, S. P., & Taylor, P. M. (2013). Pharmacokinetic and pharmacodynamic modelling of intravenous, intramuscular and subcutaneous buprenorphine in conscious cats. *Veterinary Anaesthesia and Analgesia*, *40*, 83–95.

Stewart, G. N., & Rogoff, J. M. (1922). Physiological aspects of tolerance and physical dependence. In W. S. Root & F. G. Hofmann (Eds.), *Physiological pharmacology*. Academic Press.

Streiner, D. L., & Norman, G. R. (2008). *Health measurement scales: A practical guide to their development and use*. Oxford University Press.

Sturtevant, F. M., & Drill, V. A. (1957). Tranquilizing drugs and morphinemania in cats. *Nature*, *179*, 1253.

Taguchi, K., & Suzuki, Y. (1989). Effects of microiontophoretically-applied morphine on the Purkinje cell in the cerebellum of the cat. *Neuropharmacology*, *28*, 235–242.

Taveira da Silva, A. M., Souza, J. D., Quest, J. A., Pagani, F. D., Moerschbaecher, J. M., Buller, A., Hamosh, P., & Gillis, R. A. (1983). Central nervous system site of action for the respiratory depressant effect of diacetylmorphine (heroin) in the cat. *Journal of Clinical Investigation*, *72*, 1209–1217.

Taylor, P. M., & Houlton, J. E. F. (1984). Post-operative analgesia in the dog: A comparison of morphine, buprenorphine and pentazocine. *Journal of Small Animal Practice*, *25*, 437–445.

Taylor, P. M., Kirby, J. J., Robinson, C., Watkins, E. A., Clarke, D. D., Ford, M. A., & Church, K. E. (2010). A prospective multi-Centre clinical trial to compare buprenorphine and butorphanol for postoperative analgesia in cats. *Journal of Feline Medicine and Surgery*, *12*, 247–255.

Taylor, P. M., Luangdilok, C. H., & Sear, J. W. (2016). Pharmacokinetic and pharmacodynamic evaluation of high doses of buprenorphine delivered via high-concentration formulations in cats. *Journal of Feline Medicine and Surgery*, *18*, 290–302.

Taylor, P. M., Robertson, S. A., Dixon, M. J., Ruprah, M., Sear, J. W., Lascelles, B. D., Waters, C., & Bloomfield, M. (2001). Morphine, pethidine and buprenorphine disposition in the cat. *Journal of Veterinary Pharmacology and Therapeutics*, *24*, 391–398.

Taylor, P. M., Slingsby, L. S., Pypendop, B. H., Johnson, J., & Robertson, S. A. (2007). Variable response to opioid analgesia in cats. *Veterinary Anaesthesia and Analgesia*, *34*, 6–7.

Teppema, L. J., van Dorp, E., Mousavi Gourabi, B., van Kleef, J. W., & Dahan, A. (2008). Differential effect of morphine and morphine-6-glucuronide on the control of breathing in the anesthetized cat. *Anesthesiology*, *109*, 689–697.

Terenius, L. (1973). Stereospecific interaction between narcotic analgesics and a synaptic plasm a membrane fraction of rat cerebral cortex. *Acta Pharmacologica et Toxicologica*, *32*, 317–320.

Thompson, R. C., Mansour, A., Akil, H., & Watson, S. J. (1993). Cloning and pharmacological characterization of a rat mu opioid receptor. *Neuron*, *11*, 903–913.

Traynor, J. (2012). Mu-opioid receptors and regulators of G protein signaling (RGS) proteins: From a symposium on new concepts in mu-opioid pharmacology. *Drug Alcohol Dependence*, *121*, 173–180.

Trepanier, L. A. (2006). Cytochrome P450 and its role in veterinary drug interactions. *Veterinary Clinics of North America: Small Animal Practice*, *36*, 975–985.

U.S. Department of Health and Human Services. (2008). *21 CFR 514.1 Manufacturing methods, facilities, and controls*. U.S. Department of Health and Human Services.

Vanderbist, F., Sereno, A., & Baudier, P. (2008). Stable oral pharmaceutical compositions of buprenorphine and derivatives. In M. F. Galephar (Ed.). European Patent Office.

Villiger, J. W., & Taylor, K. M. (1981). Buprenorphine: Characteristics of binding sites in the rat central nervous system. *Life Sciences*, *29*, 2699–2708.

Walker, J. M., Bowen, W. D., Thompson, L. A., Frascella, J., Lehmkuhle, S., & Hughes, H. C. (1988). Distribution of opiate receptors within visual structures of the cat brain. *Experimental Brain Research*, *73*, 523–532.

Wallenstein, M. C., & Wang, S. C. (1979). Mechanism of morphine-induced mydriasis in the cat. *American Journal of Physiology*, *236*, R292–R296.

Walsh, S. L., Preston, K. L., Stitzer, M. L., Cone, E. J., & Bigelow, G. E. (1994). Clinical pharmacology of buprenorphine: Ceiling effects at high doses. *Clinical Pharmacology & Therapeutics*, *55*, 569–580.

Walwyn, W., Sanchez-Simon, F. M., Rodriguez, R., & Evans, C. J. (2011). Delta opioid receptors. In G. Pasternak (Ed.), *The opiate recteptors*. Humana Press.

Wang, J. B., Imai, Y., Eppler, C. M., Gregor, P., Spivak, C. E., & Uhl, G. R. (1993). Mu opiate receptor: cDNA cloning and expression. *Proceedings of the National Academy of Sciences of the United States of America*, *90*, 10230–10234.

Warne, L. N., Beths, T., Carter, J. E., Whittem, T., & Bauquier, S. H. (2016). Evaluation of the influence of atipamezole on the postoperative analgesic effect of buprenorphine in cats undergoing a surgical ovariohysterectomy. *Veterinary Anaesthesia and Analgesia*, *43*, 424–428.

Warne, L. N., Beths, T., Holm, M., Carter, J. E., & Bauquier, S. H. (2014). Evaluation of the perioperative analgesic efficacy of buprenorphine, compared with butorphanol, in cats. *Journal of the American Veterinary Medical Association*, *245*, 195–202.

Wei, L., & Loh, H. H. (2011). Kappa opioid receptor gene adn regulatory mechanisms of its protein expression. In G. Pasternak (Ed.), *The opiate receptors*. Humana Press.

Wells, S. M., Glerum, L. E., & Papich, M. G. (2008). Pharmacokinetics of butorphanol in cats after intramuscular and buccal transmucosal administration. *American Journal of Veterinary Research*, *69*, 1548–1554.

Wharton, J., Polak, J. M., Pearse, A. G., McGregor, G. P., Bryant, M. G., Bloom, S. R., Emson, P. C., Bisgard, G. E., & Will, J. A. (1980). Enkephalin-, VIP- and substance P-like immunoreactivity in the carotid body. *Nature*, *284*, 269–271.

Wikler, A. (1944). Studies on the action of morphine on the central nervous system of the cat. *Journal of Pharmacology and Experimental Therapeutics*, *80*, 176.

Wolozin, B. L., & Pasternak, G. W. (1981). Classification of multiple morphine and enkephalin binding sites in the central nervous system. *Proceedings of the National Academy of Sciences of the United States of America*, *78*, 6181–6185.

Yaksh, T., & Wallace, M. (2018). Opioids, analgesia, and pain management. In L. L. Brunton, R. Hilal-Dandan, & B. C. Knollmann (Eds.), *Goodman & Gilman's the pharmacological basis of therapeutics*. McGraw Hill.

Yassen, A., Kan, J., Olofsen, E., Suidgeest, E., Dahan, A., & Danhof, M. (2007). Pharmacokinetic-pharmacodynamic modeling of the respiratory depressant effect of norbuprenorphine in rats. *Journal of Pharmacology and Experimental Therapeutics*, *321*, 598–607.

Zhang, H., Kranzler, H. R., Yang, B. Z., Luo, X., & Gelernter, J. (2008). The OPRD1 and OPRK1 loci in alcohol or drug dependence: OPRD1 variation modulates substance dependence risk. *Molecular Psychiatry*, *13*, 531–543.

Zhao, Z. Q., & Duggan, A. W. (1987). Clonidine and the hyperresponsiveness of dorsal horn neurones following morphine withdrawal in the spinal cat. *Neuropharmacology*, *26*, 1499–1502.

'Zoetis'. Solensia. https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/11817

Zoetis. (1996). Rimadyl. https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/584

'Zoetis'. Simbadol. https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/926

Zukin, R. S., Eghbali, M., Olive, D., Unterwald, E. M., & Tempel, A. (1988). Characterization and visualization of rat and Guinea pig brain kappa opioid receptors: Evidence for kappa 1 and kappa 2 opioid receptors. *Proceedings of the National Academy of Sciences of the United States of America*, *85*, 4061–4065.

How to cite this article: Clark, T. P. (2022). The history and pharmacology of buprenorphine: New advances in cats. *Journal of Veterinary Pharmacology and Therapeutics*, *45(Suppl. 1)*, 1–30. https://doi.org/10.1111/jvp.13073