Journal of the American Association for Laboratory Animal Science
Copyright 2022
by the American Association for Laboratory Animal Science
Vol 61, No 6
November 2022
Pages 597–604

A Review of Long-acting Parenteral Analgesics for Mice and Rats

Monika K. Huss* **and Cholawat Pacharinsak**

Appropriate analgesia is a crucial part of rodent postoperative and postprocedural pain. Providing appropriate analgesia is an ethical obligation, a regulatory requirement, and an essential element of obtaining quality scientific results and conducting reproducible data. Meeting these requirements is facilitated by practical, efficient and safe delivery methods for providing analgesia. Over the last decade, long-acting analgesics have gained widespread use in research animal medicine to avoid or treat postoperative or postprocedural pain while minimizing handling-related time and stress. Long-acting formulations of analgesics suitable for rodents are available for opioids, NSAIDs, and local anesthetics. The goal of this review is to summarize the currently available long-acting formulations of analgesics for rodents and to provide recommendations to veterinarians and researchers regarding their use.

Abbreviations: Bup-HCL, buprenorphine hydrochloride; Bup ER-LAB, extended-release buprenorphine by ZooPharm; Ethiqa-XR, extended-release buprenorphine by Fidelis Animal Health, Inc.; Bup-LHC, long-lasting highly concentrated buprenorphine; Meloxicam-ER, sustained-release meloxicam

DOI: 10.30802/AALAS-JAALAS-22-000061

Introduction

Treatment of pain is an ethical imperative, scientific necessity, and regulatory obligation when working with rodents in research.[34,52] Pain management involves appropriate surgical technique; the selection of effective anesthesia and analgesia regimens (including the dose, administration technique, and frequency of administration).[10,34,67] Long-acting analgesic formulations offer significant refinement for the care of rodents used for biomedical research including decreased labor and dosing time, decreased handling stress, consistent plasma drug concentrations, and clinical analgesia.[18,70] In addition, long-acting formulations also help to eliminate issues with compliance and variability in analgesic administration. Over the last 10+ years, numerous reports have studied the efficacy and duration of analgesia provided by various long-acting analgesic formulations for rodents.[2,8,20,28,30,38-40,42,53,62]

This review provides an overview of the different, but commonly used, long-acting parenteral analgesic drugs currently available for management of postoperative or procedural related pain in rats and mice in a biomedical research setting. When discussing studies evaluating the efficacy of long-acting formulations, we include the pain modality test used, sex and strain of the mouse or rat, as all of these factors can influence the analgesic efficacy of a drug.[60,68] In this review, many of the cited studies use stimulus-evoked pain testing with thermal and/or mechanical hypersensitivity testing to determine whether a long-acting analgesic formulation reduces the hypersensitivity response. Many studies use the Hargreaves test to evaluate thermal hypersensitivity. This is done by measuring the time interval between exposure of a paw to a thermal stimulus and withdrawal of the paw, which is called the heat latency response.[12] The heat latency times before (baseline) and after paw surgery and analgesic drug administration, are measured and compared.[12] A faster thermal latency after surgery indicates thermal hypersensitivity. Cited studies that evaluate mechanical hypersensitivity use the Von Frey test. In this test, the number of paw responses to a filament are measured and compared before (baseline) and again after surgery and administration of an analgesic. If the number of paw responses is higher after surgery, this is called mechanical hypersensitivity.[12] Other methods of evaluating the clinical analgesic effect of long-acting analgesic formulations include behavioral evaluation and measures of pain that are not stimulus-evoked (grimace scales, burrowing, nest building).[12]

This review is organized by the drug class and focuses on the treatment of pain with commonly used long-acting analgesics (opioids, NSAIDs, and local anesthetics) that offer analgesic coverage ranging from 12 to 96 h. For each drug class section, we provide the manufacturer's recommended dosage, current dosages evaluated in the literature, and the authors' recommendations. Specifically, the analgesics that we reviewed are extended-release buprenorphine LAB (Bup ER-LAB), extended-release buprenorphine (Ethiqa-XR), long lasting highly concentrated buprenorphine (Bup-LHC), extended-released meloxicam (Meloxicam-ER), and liposomal bupivacaine.

Formulation Technology

Long-acting formulations are available for several different analgesic classes and use different controlled-release delivery systems. These delivery systems are identified by a variety of terms, including sustained-release, extended-release, delayed-release, prolonged action, long acting, and slow release.[46] These terms are inconsistently used, named or described.[46] Most long-acting analgesic formulations use polymeric materials to provide a controlled release of the active drug so that the drug concentration remains in the therapeutic index over a

Submitted: 10 Jun 2022. Revision requested: 21 Jul 2022. Accepted: 23 Sep 2022.
Department of Comparative Medicine, Stanford University, Stanford, California
**Corresponding author. Email: monikag@stanford.edu*

longer time period.[43,46] Plasma drug level is also affected by the differences in degradation of the polymeric vehicles and the drug formulation used. For example, ZooPharm's extended-release formulations (Bup-ER and Meloxicam-ER) use a liquid polymer dissolved in a biocompatible organic solvent.[76] After injection, the drug encapsulated in the liquid polymer is released over time as the polymer undergoes biodegradation via erosion of the polymer, hydrolysis, and drug diffusion.[16] For Ethiqa-XR, another extended-release formulation of buprenorphine, buprenorphine is bound in a lipid capsule and suspended in a medium chain fatty acid triglyceride that is degraded by lipase and esterase activity.[16,49] Bup-LHC is similar to buprenorphine hydrochloride (Bup-HCL), but Bup-LHC has a higher concentration than Bup-HCL (1.8 mg/mL and 0.3 mg/mL, respectively). In addition, the vehicle for Bup-LHC consists of anhydrous dextrose, parabens, glacial acetic acid, water, and hydrochloric acid or sodium hydroxide.[45] Liposomal bupivacaine is comprised of multivesicular liposomes that encapsulate an aqueous core and bupivacaine and break down gradually over time.[24,63] Because each long-acting drug formulation has a different release technology and vehicle, the dosage and duration of analgesia provided for each formulation must be individually evaluated. To our knowledge, the vehicles for these formulations have not been tested, as companies may not be willing to make the vehicles available for research.

Long-acting buprenorphine formulations. Buprenorphine is commonly used to prevent postsurgical pain in rodents.[16,22,58] Buprenorphine is a partial µ-agonist and partial k-antagonist that relieves pain by binding to and activating the µ-opioid receptors in the central nervous system.[46] Benefits of buprenorphine administration include alleviation of moderate pain,[58] reduction in the minimum alveolar concentration (MAC) of isoflurane,[40] and a wide safety margin for rodents.[58] The primary disadvantage of Bup-HCL use is its short efficacy window, which requires repeated doses to provide extended analgesic coverage. Repeated high doses of buprenorphine can have side effects, including respiratory depression,[55,71] cardiovascular depression,[47,57] decreased blood pressure,[44,57] pica,[9,69] and decreased water consumption.[31,32,72] Bup-HCL has minimal effects on lymphoproliferation, T-cell or macrophage function, and splenic cytokine production.[11,61] Long-acting formulations of buprenorphine are currently available in an extended release formulation from ZooPharm (Bup ER-LAB), an extended release formulation from Fidelis Animal Health (Ethiqa-XR), and the Bup-LHC formulation.

Bup ER-LAB: Extended-release buprenorphine. Buprenorphine ER-LAB (Bup ER-LAB, previously labeled Bup SR-LAB) is an FDA-indexed sustained-release buprenorphine formulation that is currently available from ZooPharm (Windsor, CO) for use in mice and rats at a concentration of 0.5 mg/mL or 1 mg/mL.[75,76] The manufacturer, ZooPharm, recommends a single SC injection for mice at 0.5 to 1 mg/kg and for rats at 1 to 1.2 mg/kg, which should provide analgesia for 72 h.[75] In the literature, the effective dose and duration of analgesia provided by Bup ER-LAB for mice ranges from 0.6 to 1.5 mg/kg every 12 to 48 h depending on the strain, sex, and pain assay (Figure 1).[5,28,39] In male Swiss-Webster mice, hot plate and tail flick assays found that 1.5 mg/kg of Bup ER-LAB provided effective analgesia for 48 h.[28] In male BALB/c and SWR/J mice tested using the hot plate assay, 1 mg/kg of Bup ER-LAB provided clinically effective analgesia for 12 h.[5] In female ICR mice undergoing an experimental laparotomy, 0.6 mg/kg of Bup ER-LAB prevented pain related behaviors and provided adequate analgesia for at least 72 h.[39]

In rats, the dosage and duration of analgesia of Bup ER-LAB are reported to range from 0.3 to 1.2 mg/kg for 48 to 72 h (Figure 1).[8,20,54,62] In male Sprague–Dawley rats undergoing unicortical orthopedic surgery and hypersensitivity testing, 1.2 mg/kg of Bup ER-LAB provided analgesia for 48 to 72 h.[20] In male Sprague–Dawley rats, 0.3 mg/kg of Bup ER-LAB attenuated thermal hypersensitivity for 48 h mechanical hypersensitivity for 72 h and 1.2 mg/kg of Bup-SR attenuated both mechanical and thermal hypersensitivity for 72 h).[8] Female Sprague–Dawley rats that were treated with 1.2 mg/kg of Bup ER-LAB had effective analgesia for 48 h after a laparotomy procedure.[54] In neonatal rats (Sprague–Dawley, postnatal day 3), both low (0.5 mg/kg) and high (1 mg/kg) doses of Bup ER-LAB attenuated thermal hypersensitivity for at least 8 h in an incisional pain model.[3]

The therapeutic plasma level of buprenorphine has not been established for rodents, but plasma levels that are near 0.5 to 1 ng/mL are generally considered to be antinociceptive.[15,26,35,73] The effective therapeutic plasma level of buprenorphine was evaluated in C57BL/6J female mice using a hot plate assay; withdrawal latency was prolonged when the plasma concentration was just below 0.5 ng/mL at 4 h after injection.[35] By 8 h after injection, when the plasma concentration was 0.2 ng/mL the withdrawal latency was similar to that of saline treated mice.[35] A pharmacokinetic study of Bup ER-LAB at a dose of 0.6 mg/kg in female CD-1 mice indicated that therapeutic plasma levels of 1 ng/mL were maintained for the first 24 h but that the level fell to below 1 ng/mL by 48-h.[37] In male Sprague–Dawley rats given 0.9 mg/kg Bup ER-LAB, therapeutic plasma levels were maintained for at least 72 h. Based on the pharmacokinetic and pharmacodynamic data, we recommend dosing Bup-ER LAB at 0.6 to 1.2 mg/kg every 48 to 72 h for mice and 0.3 to 1.2 mg/kg every 48 to 72 h for rats.

Although Bup ER-LAB offers the benefits of reduced dosing frequency and a sustained analgesia level as compared with Bup-HCL, its use has different challenges. Bup ER-LAB can only be obtained with a prescription from a DEA-licensed veterinarian and cannot be ordered on a researcher's DEA license.[76] Therefore, dispensing and securing Bup ER-LAB is more complicated for the institution, researcher, and veterinarian.[51] Another challenge is obtaining the correct dosing volume, as the drug formulation is viscous, concentrated, and cannot be diluted; these factors make it difficult for researchers to administer appropriately volumes to mice.[51] Based on their findings, the authors recommended administering Bup ER-LAB with a 22-gauge needle and Leur-lock 1-mL syringe, and pinching the injection site for at least 5 s after injection to prevent drug leakage.[51] Bup ER-LAB is provided in a multidose vial and as such has been labeled with a 28-d expiration after the first puncture, even though the formulation has a 6-mo expiration date.[4] However, a recent study has found that when stored securely and accessed with aseptic technique, the vial can be maintained in a sterile state for 6 mo in a research setting.[4] Bup ER-LAB has been associated with clinical side effects that are similar to those of Bup-HCL, especially when a high dosage is used. Bup ER-LAB administration in mice has been associated with decreased GI motility,[28] increased locomotor activity (approximately 17% of mice receiving Bup ER-LAB had hyperreactivity at 24 h),[28] decreased respiratory rate,[28] and injection site lesions.[5,20] Bup ER-LAB administration in rats has also been associated with skin irritation,[20] injection site reactions,[54] pica,[54] and mild sedation.[8] Compared with Bup-HCL, Bup ER-LAB does not alter plasma levels of inflammatory cytokines MCP1 and IL6.[29] Despite the potential challenges in administration of Bup ER-LAB, its use,

Formulation and reference	Strain, species, sex	Experimental model and testing modality	Dose, route, and minimum duration of analgesia	Clinical findings
Bup ER-LAB Zoopharm Recommendations[56]	Mouse Rat		0.5–1 mg/kg SC, 72h 1–1.2 mg/kg SC, 72 h	Injection site reactions Injection site reactions
28	Male Swiss-Webster Mice	No surgery: Hot plate and tail flick assay	1.5 mg/kg SC, 48 h	Decreased GI motility until 4 h, increased activity at 4 h, reduced respiratory rate until 48 h.
6	Male BALB/cJ and SWR/J Mice	No surgery: Hot plate assay	1 mg/kg SC, 12 h	Injection site lesions
39	Female ICR Mice	Experimental laparotomy	0.6 mg/kg SC, 48 h	None
37	Female CD-1 mice	No surgery: Pharmacokinetics study	0.6 mg/kg SC, 24 h	None
20	Male Sprague–Dawley rats	Unicortical tibial defect and thermal nociception	1.2 mg/kg SC, 48 to 72 h	Skin irritation
9	Male Sprague–Dawley rats	Paw incision	0.3 and 1.2 mg/kg SC, 48–72 h	Mild sedation
20	Male Sprague–Dawley	No surgery: Pharmacokinetic study	0.9 mg/kg SC, 72 h	Skin irritation
62	Male Sprague–Dawley rats	Paw incision	1.2 mg/kg SC, 96 h	None
54	Female Sprague–Dawley rats	Laparotomy	1.2 mg/kg SC. 48 h	Pica and injection site reactions
4	P3 male and female Sprague–Dawley rats	Incisional pain	0.5 or 1 mg/kg, 8 h	None
Ethiqa-XR Fidelis Animal Health Recommendations[16]	Mouse Rat		3.25 mg/kg SC, 72 h 0.65 mg/kg SC, 72 h	Signs of nausea, including self-licking, self-gnawing and eating wood chip bedding
53	Male C57BL/6J mice	Incisional pain and pharmacokinetics	3.25 or 6.5 mg/kg SC, 48 h	Hyperreactivity
8	Male and female C57BL/6J mice	Laparotomy and pharmacokinetics	3.25 mg/kg SC, 24–48 h	None
3	Male Sprague–Dawley rats	Incisional pain and pharmacokinetics	0.65 mg/kg or 1.3 mg/kg SC, 48 h	Sedation
42	Male and female Sprague–Dawley rats	Pharmacokinetics	0.65 mg or 1.3 mg/kg SC, 72 h	Injection site reaction
Bup-LHC Zoetis Recommendations[74]	Cat		0.24 mg/kg SC, 24 h	Hyperactivity in cats
38	Male C57BL/6J and female CD1 mice	Pharmacokinetics of B6 and CD1 mice, experimental laparotomy for CD1 females	0.9 mg/kg SC, 6 h	None
51	Male and female C57BL/6NCrl mice	Pharmacokinetics	1 mg/kg SC, 12 h	Ataxia, Straub tail reaction and tiptoe gait
30	Male and female Sprague–Dawley rats	Mechanical pain testing, laparotomy, and pharmacokinetics	0.5 mg/kg SC, 12–24 h	Sedation, coprophagy
Meloxicam-ER Zoopharm Recommendations[75]	Rat		4 mg/kg SC, 72 h	GI distress
37	Female CD-1 mice	Pharmacokinetics	6 mg/kg SC, 12 h	None

Figure 1. Summary of the cited studies evaluating the efficacy of long-acting analgesics for mice or rats.

48	Male Swiss-Webster	Surgical osmotic pump implantation and pharmacokinetics	4 mg/kg SC, was not efficacious	Injection site reactions
62	Male Sprague–Dawley rats	Paw incision	4 mg/kg SC, 96 h (mechanical hypersensitivity only)	None
66	Male and female Sprague–Dawley rats	N/A	N/A	Injection site reactions
Liposomal bupivacaine Pacira Biosciences Recommendations[56]	Human		Max dose based on size of surgical site or 4 mg/kg for pediatric patients	Nausea, constipation, and vomiting
25	Male Swiss-Webster mice	No surgery: electrical sensory stimulus to the abdomen	0.2 mL of 0.5%, 1% and 2% local infiltration in a 26-g mouse provide analgesia for 3, 6 and 26 h	None
Exparel[36]	Male Sprague–Dawley Rats	Paw incision	1 mg/kg local infiltration, 96 h	None
Nocita Elanco Recommendations[1]	Dogs		5.3 mg/kg local infiltration, 72 h	Discharge, inflammation, vomiting

Figure 1. (Continued)

as compared with Bup-HCL, offers a significant refinement for rodent analgesia by providing more consistent long-lasting analgesia with limited administration challenges or untoward clinical effects.

Ethiqa-XR: Extended-release buprenorphine. Extended-release buprenorphine (Ethiqa-XR) from Fidelis Animal Health is an FDA-indexed long-acting buprenorphine that is available at a concentration of 1.3 mg/mL.[16] The dose recommendations of Ethiqa-XR for mice and rats differ from that of Bup ER-LAB, as the 2 formulations use different technologies that affect the rate of drug release (Figure 1). The manufacturer's recommended dose is 3.25 mg/kg for mice and 0.65 mg/kg for rats every 72 h.[14] Recent studies have supported these dosage recommendations for mice and rats. A study that evaluated the clinical efficacy of Ethiqa-XR using an incisional pain model in male C57BL/6J mice at 3.25 or 6.5 mg/kg found effective attenuation of mechanical hypersensitivity and therapeutic plasma levels of at least 1 ng/mL for 48 h.[53] Another study evaluated the efficacy of Ethiqa-XR at 3.25 mg/kg using a laparotomy model in male and female C57BL/6J mice and found that Ethiqa-XR treatment mice had lower ethogram scores at 6 and 12 h after surgery.[7] In this same study, pharmacokinetic analysis of male C57BL6/J mice found that plasma buprenorphine concentration was above 1 ng/mL from 30 min to 48 h after administration.[7] A study using male Sprague–Dawley rats in an incisional pain model found that mechanical hypersensitivity was attenuated for at least 48 h after a dose of 0.65 or 1.3 mg/kg of Ethiqa-XR.[2] The same study found that a dose of 0.65 or 1.3 mg/kg of Ethiqa-XR provided a buprenorphine plasma concentration above 1 ng/mL for 24 h and above 0.5 ng/mL for 72 h.[2] Another pharmacokinetic study in male and female Sprague–Dawley rats given a dose of 0.65 or 1.3 mg/kg also reported buprenorphine plasma concentration above 1 ng/mL at 24 h and above 0.5 ng/mL for 72 h in both male and female rats, although female rats had lower mean buprenorphine plasma concentrations as compared with males.[42] Taking into account the manufacturer's recommended dose and literature results, we recommend dosing Ethiqa-XR SC at 3.25 mg/kg for mice and 0.65 mg/kg for rats every 48 to 72 h.

Ethiqa-XR has many of the same usage challenges described above for Bup ER-LAB. Like Bup ER-LAB, Ethiqa-XR cannot be diluted and has a small administration volume for mice (25-g mouse = 0.07 mL for a 3.25 mg/kg dose). Even though Ethiqa-XR is less viscous than Bup ER-LAB, we recommend injecting it with a 22-gauge needle and a Leur-lock 1-mL syringe. The Ethiqa-XR vial should be mixed before dosing to ensure even drug distribution.[16] Like Bup ER-LAB, the injection site should be pinched for 5 s after administration to prevent drug leakage.[53] A benefit of Ethiqa-XR as compared with Bup ER-LAB is that Ethiqa-XR can currently be purchased from distributors with a researcher DEA license. The only untoward side effect reported after administration of Ethiqa-XR to mice is hyperreactivity (over 50% of study mice exhibited hyperreactivity at 24 h).[53] Untoward clinical effects reported in rats included mild sedation and injection-site reactions.[2,42] Like Bup ER-LAB, Ethiqa-XR also offers a significant refinement over Bup-HCL, and because it is available with a researcher DEA license, procurement and management may be easier distribution as compared with Bup ER-LAB.

Bup-LHC: Long-lasting highly concentrated buprenorphine. Long-lasting highly-concentrated formulation Bup-LHC (commercially available as Simbadol) is FDA-approved and labeled as providing 24 h of analgesia for cats.[74] According to the manufacturer (Zoetis), the recommended dose for cats is 0.24 mg/kg once daily for up to 3 d.[74] Bup-LHC is considered an immediate-release product, which means that buprenorphine is quickly absorbed after subcutaneous injection.[74] Based on the literature, we recommend dosing mice at 0.9 to 1 mg/kg SC every 6 to 12 h (Figure 1).[38,51] Bup-LHC at 0.9 mg/kg provided at least 6 h of decreased pain behaviors in female ICR mice after experimental laparotomy.[38] In male and female C57BL/6NCrl mice, Bup-LHC at 1 mg/kg maintained therapeutic plasma levels of buprenorphine for 12 h, but was below the therapeutic level at 16 h.[51] Based on the literature, we recommend dosing rats with Bup-LHC at 0.5 mg/kg every 12 to 24 h. In male and female Sprague–Dawley rats, Bup-LHC at 0.5 mg/kg provided clinical analgesia for at least 12 h, as evaluated by mechanical pain tolerance and experimental laparotomy.[30] A buprenorphine plasma concentration above

1 ng/mL was maintained for just under 24 h in male and over 24 h in female Sprague–Dawley rats.[30]

Bup-LHC is available from veterinary drug distributors and can be purchased with a researcher DEA license. Although Bup-LHC is highly concentrated, the solution is not viscous like Bup ER-LAB or Ethiqa-XR so it can be dosed with a 25-gauge needle. Behavior changes noted in mice after Bup-LHC administration include mild ataxia, Straub tail reaction, and a tiptoe gait.[51] In rats, untoward clinical effects included sedation and coprophagy.[30] Although the therapeutic plasma concentration and clinical efficacy of Bup-LHC last longer than that of Bup-HCL, both Bup ER-LAB and Ethiqa-XR formulations provide longer periods of analgesia and practical, compliance, and welfare advantages as compared with Bup-LHC.

Long-acting NSAIDs. Several NSAIDs are available for analgesia in rodents with varying durations of effect, including carprofen (12 to 24 h), meloxicam (12 h), ketoprofen (24 h), ibuprofen (not determined), and acetaminophen (not determined).[17,19] NSAIDs exert their main effect by inhibiting the action of the enzyme cyclooxygenase (COX) and mediating the process of inflammation.[17] Typically, NSAIDs are considered to provide less analgesic strength than opioids, but are useful for managing mild pain and inflammatory conditions (such as arthritis), and as part of a multimodal analgesic regimens with opioids.[17] A review of recent literature[19] suggests that commonly used dosing regimens for NSAIDs in rodents likely do not match the duration of effective analgesia or therapeutic plasma levels.[19] For example, one study found that carprofen given to mice at 5 mg/kg SC provided effective analgesia for 6 to 12 h, but the dosing interval often used is every 24 h.[19,37,59] NSAID use, especially at a higher dosing frequency, can increase the risk of untoward clinical effects[17] including gastrointestinal disturbances, nephrotoxicity, interference with platelet function, blood dyscrasias, liver toxicity, ulceration,[64] and hemorrhage.[64] Long-acting NSAIDs are attractive as they offer a sustained therapeutic concentration without the risk of adverse effects. Currently, one commercially available long-acting NSAID, sustained-release meloxicam, is available for use in rodents.

Meloxicam-ER: Extended-release meloxicam. Extended-release meloxicam (Melox-ER) is an FDA-indexed drug that is available from ZooPharm at a concentration of 2 mg/mL.[76] ZooPharm recommends a dose of Meloxicam-ER of 4 mg/kg every 72 h for rats. One study has evaluated Meloxicam-ER at 4 mg/kg in male Sprague–Dawley rats; this study found that this therapy attenuated mechanical hypersensitivity (but not thermal hypersensitivity) for 96 h in an incisional pain model.[62] Injection site reactions have been reported as an untoward clinical effect of Meloxicam-ER in Sprague–Dawley rats.[66] ZooPharm does not have a label recommendation for the dose of Meloxicam-ER in mice.[76] One study[1] evaluated the clinical efficacy of 4 mg/kg of Meloxicam-ER during surgical osmotic pump placement in male Swiss Webster mice and found that the mice showed behavioral indications of pain and insufficient plasma drug concentration at 4 h after administration.[48] Injection site reactions occurred in some of the mice that received Meloxicam-ER.[48] Injection site reactions were also noted and slowly resolved after Meloxicam-ER administration in multiple strains of mice (Crl:CD1(ICR), C57BL/6J, and BALB/cJ).[21]

The therapeutic plasma level of meloxicam is currently unknown, but based on studies in cats,[23] dogs,[33] and horses[41] it is estimated to be between 390 and 911 ng/mL. In Sprague–Dawley rats, 4 mg/kg of Meloxicam-ER provided a plasma concentration that was highest on day 1 (1,800 ng/mL), lower on day 2 (500 ng/mL), and subsequently lower thereafter.[62] In female CD1 mice, Meloxicam-ER dosed at 6 mg/kg provided a plasma level above 1,000 ng/mL for the 12 h after administration.[37] Another study[1] also evaluated a dose of 6 mg/kg of Meloxicam-ER in female CD1 mice and found that plasma levels remained above the estimated therapeutic level (390 to 911 ng/mL) for the first 12 h without any incidence of clinical signs.[37]

Meloxicam-ER can also be administered using a slow-release technology consisting of a lipid polymer encapsulation of the drug.[76] This lipid polymer produces a highly viscous solution, making drug preparation and injection more difficult.[62] We recommend administering Meloxicam-ER with a 22-gauge needle and Leur-lock 1-mL syringe and pinching the injection site for at least 5 s after administration to prevent drug leakage. Further evaluation of the clinical efficacy of Meloxicam-ER in mice is needed, as the plasma concentration measurements indicate that the therapeutic level is maintained for 12 h, but pharmacodynamic studies present conflicting results. For rats, we suggest using Meloxicam-ER at a dose of 4 mg/kg every 96 h.

Long-acting local anesthetics. Local anesthetics provide a quick onset of action, minimal side effects, large therapeutic index, reduced intraoperative bleeding with vasoconstriction, and a predictable duration of action.[65] A review of preemptive analgesic practices[50] notes that the disadvantage of local anesthetics is typically that they offer only a short therapeutic window (< 8 h) that does not extend for long into the postoperative period after a surgical procedure.[50] Local anesthetics with a long duration can decrease the postoperative pain and, in some situations, may be the only analgesic required or may be a critical component of a multimodal analgesic regimen.

Liposomal bupivacaine. Liposomal bupivacaine is a slow-release bupivacaine formulation that can provide extended postoperative analgesia after single-dose administration.[24,27,63] An experimental drug formulation of liposomal bupivacaine (0.2 mL of 0.5, 1, or 2% liposomal bupivacaine) was evaluated on a marked location of the abdomen in male Swiss-Webster mice.[25] At 24 h after injection, approximately 20% to 30% of the initial concentration remained at the injection site and could still be detected at 48 h.[25] The duration of analgesic response time as determined by monitoring the vocalization response to an electrical stimulus was 3, 6, and 26 h for mice injected with 0.2 mL of 0.5, 1, and 2% liposomal bupivacaine, respectively.[25] No untoward clinical signs were noted in mice.[25] Exparel is a commercially available formulation of liposomal bupivacaine (13.3 mg/mL) that was first approved by the FDA in 2011 for postsurgical pain management in humans; the recommended dose for human patients under the age of 17 is 4 mg/kg.[13] One study reported that local infiltration of liposomal bupivacaine (Exparel) at a dose of 1 mg/kg SC attenuated postoperative mechanical and thermal hypersensitivity for 96 h in rats with incisional pain.[36] Based on the clinical efficacy of Exparel for the attenuation of hypersensitivity, we recommend dosing liposomal bupivacaine at 1 mg/kg to provide up to 96 h of local anesthesia.

A veterinary product, Nocita, was approved by the FDA in 2016 for use in dogs and cats at a dosage of 5.3 mg/kg.[14] Nocita is also formulated with 13.3 mg/mL of bupivacaine.[14] Nocita and Exparel are both currently available in 10-mL or 20-mL, single-use vials.[14] The label states that liposomal bupivacaine can be stored in a syringe at a room temperature of 68 to 77 °F (20 to 25 °C) for a maximum of 4 h.[14] Another study evaluated 5 d of repeated sterile withdrawal from single-use vials and found that Nocita could be used for up to 96 h when stored either under refrigeration or at room temperature.[6] Liposomal bupivacaine should be administered by infiltration of all incised

Drug	Mouse: dosage and duration	Rat: dosage and duration
Bup ER-LAB	0.6–1.2 mg/kg, 48–72 h	0.3–1.2 mg/kg, 48–72 h
Ethiqa-XR	3.25 mg/kg, 48–72 h	0.65 mg/kg, 48–72 h
Meloxicam-ER	Further evaluation needed	4 mg/kg, 72–96 h
Liposomal bupivacaine	1 mg/kg (local infiltration), 96 h	1 mg/kg (local infiltration), 96 h

Figure 2. Summary of the authors' recommendations for dosage and duration of analgesia provided by long-acting analgesics for mice and rats. The dosage chosen will depend on the model being studied, expected pain, strain, sex, and other analgesics or anesthetics used.

tissue layers prior to closure of the surgical site.[14,56] If the dose volume too small to cover the surgical site, an equal volume of normal (0.9%) sterile saline or Lactated Ring's solution[14,56] can be added. Due to the small administration volume, price, and need to discard soon after opening, use of Nocita and Exparel can be financially challenging (a 10-mL vial costs approximately $180 USD). However, for studies in which opioids and/or NSAIDs are contraindicated, Nocita should be considered for analgesia.

Conclusions

Long-acting parenteral analgesics offer the benefits of an extended duration of analgesia, less handling stress, and lower risk of untoward clinical effects. Bup ER-LAB and Ethiqa-XR, extended-release buprenorphine formulations are practical options that have been shown to be clinically efficacious in both mice and rats (Figure 2). An additional benefit of Ethiqa-XR is that it can be procured with a research DEA license instead of a veterinary license. However, Ethiqa-XR is also more expensive than Bup ER-LAB. One dose of Bup ER-LAB (1.2 mg/kg SC) for a 300 g rat costs $8.28 USD, and Ethiqa-XR (0.65 mg/kg SC) costs $18.75 USD. For a 25-g mouse, one dose of Bup ER-LAB (1 mg/kg SC) costs $1.56 US, whereas Ethiqa-XR (3.25mg/kg SC) costs $8.75 USD. Meloxicam-ER has been evaluated less extensively than long-acting buprenorphine formulations; for rats, current data indicate Meloxicam-ER is clinically efficacious, but more evaluation is needed for mice. Nocita and Exparel are the most expensive (at over $180 USD per vial) but are good options for studies that require multimodal analgesia or those for which opioids and/or NSAIDs are contraindicated.

The choice of an analgesic regimen, including analgesic type, dosage regimen, and method of administration, must consider the model, study objectives, anesthetic method, sex, species, and strain. All these factors can affect the dose and duration of analgesia. Additional studies are needed to determine whether long-acting formulations could replace other short-acting opioids (such as morphine, fentanyl, oxymorphone, or butorphanol) or NSAIDs (such as ibuprofen, ketorolac, celecoxib, diclofenac, or parecoxib) for rodents and to determine how long-acting formulations can be used as a part of a multimodal analgesia regimen.

Acknowledgments

We are grateful for the assistance of Janis Atuk-Jones for formatting and reviewing the manuscript.

References

1. **Adamson TW, Kendall LV, Goss S, Grayson K, Touma C, Palme R, Chen JQ, Borowsky AD.** 2010. Assessment of carprofen and buprenorphine on recovery of mice after surgical removal of the mammary fat pad. J Am Assoc Lab Anim Sci **49:**610–616.
2. **Alamaw ED, Franco BD, Jampachaisri K, Huss MK, Pacharinsak C.** 2022. Extended-release Buprenorphine, an FDA-indexed Analgesic, Attenuates Mechanical Hypersensitivity in Rats (*Rattus norvegicus*). J Am Assoc Lab Anim Sci **61:**81–88. https://doi.org/10.30802/AALAS-JAALAS-21-000081.
3. **Blaney A, Jampachaisri K, Huss MK, Pacharinsak C.** 2021. Sustained release buprenorphine effectively attenuates postoperative hypersensitivity in an incisional pain model in neonatal rats (*Rattus norvegicus*). PLoS One **16:**e0246213. https://doi.org/10.1371/journal.pone.0246213.
4. **Cantara SI, Gergye C, Lee VK, Huerkamp M.** 2022. Sterility of sustained-release buprenorphine. J Am Assoc Lab Anim Sci **61:**208–210. https://doi.org/10.30802/AALAS-JAALAS-21-000105.
5. **Carbone ET, Lindstrom KE, Diep S, Carbone L.** 2012. Duration of action of sustained-release buprenorphine in 2 strains of mice. J Am Assoc Lab Anim Sci **51:**815–819.
6. **Carlson AR, Nixon E, Jacob ME, Messenger KM.** 2020. Sterility and concentration of liposomal bupivacaine single-use vial when used in a multiple-dose manner. Vet Surg **49:**772–777. https://doi.org/10.1111/vsu.13380.
7. **Chan G, Si C, Nichols MR, Kennedy L.** 2022. Assessment of the safety and efficacy of pre-emptive use of extended-release buprenorphine for mouse laparotomy. J Am Assoc Lab Anim Sci **61:**381–387. https://doi.org/10.30802/AALAS-JAALAS-22-000021.
8. **Chum HH, Jampachairsri K, McKeon GP, Yeomans DC, Pacharinsak C, Felt SA.** 2014. Antinociceptive effects of sustained-release buprenorphine in a model of incisional pain in rats (*Rattus norvegicus*). J Am Assoc Lab Anim Sci **53:**193–197.
9. **Clark JA Jr, Myers PH, Goelz MF, Thigpen JE, Forsythe DB.** 1997. Pica behavior associated with buprenorphine administration in the rat. Lab Anim Sci **47:**300–303.
10. **Corona R, Verguts J, Binda MM, Molinas CR, Schonman R, Koninckx PR.** 2011. The impact of the learning curve on adhesion formation in a laparoscopic mouse model. Fertil Steril **96:**193–197. https://doi.org/10.1016/j.fertnstert.2011.04.057.
11. **Cotroneo TM, Hugunin KM, Shuster KA, Hwang HJ, Kakaraparthi BN, Nemzek-Hamlin JA.** 2012. Effects of buprenorphine on a cecal ligation and puncture model in C57BL/6 mice. J Am Assoc Lab Anim Sci **51:**357–365.
12. **Deuis JR, Dvorakova LS, Vetter I.** 2017. methods used to evaluate pain behaviors in rodents. Front Mol Neurosci **10:**284. https://doi.org/10.3389/fnmol.2017.00284.
13. **Eberle N, Newman M.** 2015. Patient perception of postoperative pain after administration of liposomal bupivacaine in plastic surgery. Ann Plast Surg **74:**S198–S200. https://doi.org/10.1097/SAP.0000000000000444.
14. **Elanco.** [Internet] 2021. Nocita (bupivane liposome injectable suspension). [Cited 04 May 2022]. Available at: https://www.elancolabels.com/us/nocita.
15. **Evans HC, Easthope SE.** 2003. Transdermal buprenorphine. Drugs **63:**1999–2010. https://doi.org/10.2165/00003495-200363190-00003.
16. **Fidelis Animal Health.** [Internet]. 2018. Ethiqa XR (buprenorphine extended-release injectable suspension) 1.3 mg/mL. [Cited 20 June 2022]. Available at: https://ethiqaxr.com/efficacy-and-safety/.
17. **Flecknell PA.** 2016. Laboratory animal anaesthesia, Fourth edition. Boston (MA): Elsevier.
18. **Foley PL.** 2014. Current options for providing sustained analgesia to laboratory animals. Lab Anim (NY) **43:**364–371. https://doi.org/10.1038/laban.590.
19. **Foley PL, Kendall LV, Turner PV.** 2019. Clinical management of pain in rodents. Comp Med **69:**468–489. https://doi.org/10.30802/AALAS-CM-19-000048.
20. **Foley PL, Liang H, Crichlow AR.** 2011. Evaluation of a sustained-release formulation of buprenorphine for analgesia in rats. J Am Assoc Lab Anim Sci **50:**198–204.
21. **Fuetsch SR, Stewart LA, Imai DM, Beckett LA, Li Y, Lloyd KCK, Grimsrud KN.** 2021. Injection Reactions after Administration of Sustained-release Meloxicam to BALB/cJ, C57BL/6J, and

Crl:CD1(ICR) Mice. J Am Assoc Lab Anim Sci **60:**176–183. https://doi.org/10.30802/AALAS-JAALAS-20-000042.
22. **Gaertner DJ, Hallman TM, Hankenson FC, Batchelder MA.** Chapter 10 - Anesthesia and Analgesia for Laboratory Rodents, p 239–297. In: Fish RE, Brown MJ, Danneman PJ, Karas AZ, editors. Anesthesia and Analgesia in Laboratory Animals (Second Edition). San Diego (CA): Academic Press.
23. **Giraudel JM, Diquelou A, Laroute V, Lees P, Toutain PL.** 2005. Pharmacokinetic/pharmacodynamic modelling of NSAIDs in a model of reversible inflammation in the cat. Br J Pharmacol **146:**642–653. https://doi.org/10.1038/sj.bjp.0706372.
24. **Golembiewski J, Dasta J.** 2015. Evolving role of local anesthetics in managing postsurgical analgesia. Clin Ther **37:**1354–1371. https://doi.org/10.1016/j.clinthera.2015.03.017.
25. **Grant GJ, Piskoun B, Bansinath M.** 2003. Analgesic duration and kinetics of liposomal bupivacaine after subcutaneous injection in mice. Clin Exp Pharmacol Physiol **30:**966–968. https://doi.org/10.1111/j.1440-1681.2003.03933.x.
26. **Guarnieri M, Brayton C, DeTolla L, Forbes-McBean N, Sarabia-Estrada R, Zadnik P.** 2012. Safety and efficacy of buprenorphine for analgesia in laboratory mice and rats. Lab Anim (NY) **41:**337–343. https://doi.org/10.1038/laban.152.
27. **Hadzic A, Abikhaled JA, Harmon WJ.** 2015. Impact of volume expansion on the efficacy and pharmacokinetics of liposome bupivacaine. Local Reg Anesth **8:**105–111. https://doi.org/10.2147/LRA.S88685.
28. **Healy JR, Tonkin JL, Kamarec SR, Saludes MA, Ibrahim SY, Matsumoto RR, Wimsatt JH.** 2014. Evaluation of an improved sustained-release buprenorphine formulation for use in mice. Am J Vet Res **75:**619–625. https://doi.org/10.2460/ajvr.75.7.619.
29. **Herndon NL, Bandyopadhyay S, Hod EA, Prestia KA.** 2016. Sustained-release buprenorphine improves postsurgical clinical condition but does not alter survival or cytokine levels in a murine model of polymicrobial sepsis. Comp Med **66:**455–462.
30. **Houston ER, Tan SM, Thomas SM, Stasula UL, Burton MK, Knych HK, Kendall LV.** 2021. Pharmacokinetics and efficacy of a long-lasting, highly concentrated buprenorphine solution in rats. J Am Assoc Lab Anim Sci **60:**667–674. https://doi.org/10.30802/AALAS-JAALAS-21-000055.
31. **Hutchings DE, Zmitrovich AC, Hamowy AS, Liu PY.** 1995. Prenatal administration of buprenorphine using the osmotic minipump: a preliminary study of maternal and offspring toxicity and growth in the rat. Neurotoxicol Teratol **17:**419–423. https://doi.org/10.1016/0892-0362(94)00079-S.
32. **Jessen L, Christensen S, Bjerrum OJ.** 2007. The antinociceptive efficacy of buprenorphine administered through the drinking water of rats. Lab Anim **41:**185–196. https://doi.org/10.1258/002367707780378131.
33. **Jeunesse EC, Bargues IA, Toutain CE, Lacroix MZ, Letellier IM, Giraudel JM, Toutain PL.** 2011. Paw inflammation model in dogs for preclinical pharmacokinetic/pharmacodynamic investigations of nonsteroidal anti-inflammatory drugs. J Pharmacol Exp Ther **338:**548–558. https://doi.org/10.1124/jpet.110.178350.
34. **Jirkof P.** 2017. Side effects of pain and analgesia in animal experimentation. Lab Anim (NY) **46:**123–128. https://doi.org/10.1038/laban.1216.
35. **Jirkof P, Tourvieille A, Cinelli P, Arras M.** 2015. Buprenorphine for pain relief in mice: repeated injections vs sustained-release depot formulation. Lab Anim **49:**177–187. https://doi.org/10.1177/0023677214562849.
36. **Kang SC, Jampachaisri K, Seymour TL, Felt SA, Pacharinsak C.** 2017. Use of liposomal bupivacaine for postoperative analgesia in an incisional pain model in rats (*Rattus norvegicus*). J Am Assoc Lab Anim Sci **56:**63–68.
37. **Kendall LV, Hansen RJ, Dorsey K, Kang S, Lunghofer PJ, Gustafson DL.** 2014. Pharmacokinetics of sustained-release analgesics in mice. J Am Assoc Lab Anim Sci **53:**478–484.
38. **Kendall LV, Singh B, Bailey AL, Smith BJ, Houston ER, Patil K, Doane CJ.** 2021. Pharmacokinetics and efficacy of a long-lasting, highly concentrated buprenorphine solution in mice. J Am Assoc Lab Anim Sci **60:**64–71. https://doi.org/10.30802/AALAS-JAALAS-20-000049.
39. **Kendall LV, Wegenast DJ, Smith BJ, Dorsey KM, Kang S, Lee NY, Hess AM.** 2016. Efficacy of sustained-release buprenorphine in an experimental laparotomy model in female mice. J Am Assoc Lab Anim Sci **55:**66–73.
40. **LaTourette PC, David EM, Pacharinsak C, Jampachaisri K, Smith JC, Marx JO.** 2020. Effects of standard and sustained-release buprenorphine on the minimum alveolar concentration of isoflurane in C57BL/6 mice. J Am Assoc Lab Anim Sci **59:**298–304. https://doi.org/10.30802/AALAS-JAALAS-19-000106.
41. **Lees P, Giraudel J, Landoni MF, Toutain PL.** 2004. PK-PD integration and PK-PD modelling of nonsteroidal anti-inflammatory drugs: principles and applications in veterinary pharmacology. J Vet Pharmacol Ther **27:**491–502. https://doi.org/10.1111/j.1365-2885.2004.00618.x.
42. **Levinson BL, Leary SL, Bassett BJ, Cook CJ, Gorman GS, Coward LU.** 2021. Pharmacokinetic and histopathologic study of an extended-release, injectable formulation of buprenorphine in Sprague-Dawley rats. J Am Assoc Lab Anim Sci **60:**462–469. https://doi.org/10.30802/AALAS-JAALAS-20-000149.
43. **Liechty WB, Kryscio DR, Slaughter BV, Peppas NA.** 2010. Polymers for drug delivery systems. Annu Rev Chem Biomol Eng **1:**149–173. https://doi.org/10.1146/annurev-chembioeng-073009-100847.
44. **Lutfy K, Eitan S, Bryant CD, Yang YC, Saliminejad N, Walwyn W, Kieffer BL, Takeshima H, Carroll FI, Maidment NT, Evans CJ.** 2003. Buprenorphine-induced antinociception is mediated by mu-opioid receptors and compromised by concomitant activation of opioid receptor-like receptors. J Neurosci **23:**10331–10337. https://doi.org/10.1523/JNEUROSCI.23-32-10331.2003.
45. **Mackiewicz AL, Salyards GW, Knych HK, Hill AE, Christe KL.** 2019. Pharmacokinetics of a long-lasting, highly concentrated buprenorphine solution after subcutaneous administration in rhesus macaques (*Macaca mulatta*). J Am Assoc Lab Anim Sci **58:**501–509. https://doi.org/10.30802/AALAS-JAALAS-18-000115.
46. **Martin C, De Baerdemaeker A, Poelaert J, Madder A, Hoogenboom R, Ballet S.** 2016. Controlled-release of opioids for improved pain management. Mater Today **19:**491–502. https://doi.org/10.1016/j.mattod.2016.01.016.
47. **Martinez EA, Hartsfield SM, Melendez LD, Matthews NS, Slater MR.** 1997. Cardiovascular effects of buprenorphine in anesthetized dogs. Am J Vet Res **58:**1280–1284.
48. **Mexas A, Herrod J, Veltri C, Doane C.** 2017. Inappropriate postoperative analgesia is achieved using recommended doses of sustained-release meloxicam in mice. J Anim Health Behav Sci **1:**109.
49. **Mishra DK, Dhote V, Bhatnagar P, Mishra PK.** 2012. Engineering solid lipid nanoparticles for improved drug delivery: promises and challenges of translational research. Drug Deliv Transl Res **2:**238–253. https://doi.org/10.1007/s13346-012-0088-9.
50. **Møiniche S, Kehlet H, Dahl JB.** 2002. A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: The role of timing of analgesia. Anesthesiology **96:**725–741. https://doi.org/10.1097/00000542-200203000-00032.
51. **Myers PH, Goulding DR, Wiltshire RA, McGee CA, Dickerson AB, Comins MM, Shi M, Kissling GE, Lih FB, Deterding LJ, Laber-Laird KE, Blankenship-Paris TL.** 2021. Serum buprenorphine concentrations and behavioral activity in mice after a single subcutaneous injection of simbadol, buprenorphine SR-LAB, or standard buprenorphine. J Am Assoc Lab Anim Sci **60:**661–666. https://doi.org/10.30802/AALAS-JAALAS-21-000028.
52. **National Research Council.** 2011. Guide for the care and use of laboratory animals, 8th edition. Washington (DC): The National Academies Press.
53. **Navarro K, Jampachaisri K, Huss M, Pacharinsak C.** 2021. Lipid bound extended release buprenorphine (high and low doses) and sustained release buprenorphine effectively attenuate post-operative hypersensitivity in an incisional pain model in mice (*Mus musculus*). Animal Model Exp Med **4:**129–137. https://doi.org/10.1002/ame2.12157.
54. **Nunamaker EA, Goldman JL, Adams CR, Fortman JD.** 2018. Evaluation of analgesic efficacy of meloxicam and 2 formulations of buprenorphine after laparotomy in female Sprague-Dawley rats. J Am Assoc Lab Anim Sci **57:**498–507. https://doi.org/10.30802/AALAS-JAALAS-17-000129.

55. **Ohtani M, Kotaki H, Nishitateno K, Sawada Y, Iga T.** 1997. Kinetics of respiratory depression in rats induced by buprenorphine and its metabolite, norbuprenorphine. J Pharmacol Exp Ther **281:**428–433.
56. **Pacira Biosciences Inc.** [Internet]. 2022. Non-opioid Exparel (bupivicaine liposome injectable suspension). [Cited 01 August 2022]. Available at: https://www.exparel.com/.
57. **Rätsep MT, Barrette VF, Winterborn A, Adams MA, Croy BA.** 2013. Hemodynamic and behavioral differences after administration of meloxicam, buprenorphine, or tramadol as analgesics for telemeter implantation in mice. J Am Assoc Lab Anim Sci **52:**560–566.
58. **Roughan JV, Flecknell PA.** 2002. Buprenorphine: a reappraisal of its antinociceptive effects and therapeutic use in alleviating post-operative pain in animals. Lab Anim **36:**322–343. https://doi.org/10.1258/002367702320162423.
59. **Roughan JV, Flecknell PA.** 2004. Behaviour-based assessment of the duration of laparotomy-induced abdominal pain and the analgesic effects of carprofen and buprenorphine in rats. Behav Pharmacol **15:**461–472. https://doi.org/10.1097/00008877-200411000-00002.
60. **Rudeck J, Vogl S, Heinl C, Steinfath M, Fritzwanker S, Kliewer A, Schulz S, Schönfelder G, Bert B.** 2020. Analgesic treatment with buprenorphine should be adapted to the mouse strain. Pharmacol Biochem Behav **191:**172877. https://doi.org/10.1016/j.pbb.2020.172877.
61. **Sacerdote P.** 2006. Opioids and the immune system. Palliat Med **20:**S9–S15. https://doi.org/10.1191/0269216306pm1124oa.
62. **Seymour TL, Adams SC, Felt SA, Jampachaisri K, Yeomans DC, Pacharinsak C.** 2016. Postoperative analgesia due to sustained-release buprenorphine, sustained-release meloxicam, and carprofen gel in a model of incisional pain in rats (*Rattus norvegicus*). J Am Assoc Lab Anim Sci **55:**300–305.
63. **Shah J, Votta-Velis EG, Borgeat A.** 2018. New local anesthetics. Best Pract Res Clin Anaesthesiol **32:**179–185. https://doi.org/10.1016/j.bpa.2018.06.010.
64. **Shientag LJ, Wheeler SM, Garlick DS, Maranda LS.** 2012. A therapeutic dose of ketoprofen causes acute gastrointestinal bleeding, erosions, and ulcers in rats. J Am Assoc Lab Anim Sci **51:**832–841.
65. **Sisk AL.** 1992. Long-acting local anesthetics in dentistry. Anesth Prog **39:**53–60.
66. **Stewart LA, Imai DM, Beckett L, Li Y, Lloyd KC, Grimsrud KN.** 2020. Injection-site reactions to sustained-release meloxicam in Sprague–Dawley rats. J Am Assoc Lab Anim Sci **59:**726–731. https://doi.org/10.30802/AALAS-JAALAS-20-000014.
67. **Stulberg JJ, Huang R, Kreutzer L, Ban K, Champagne BJ, Steele SR, Johnson JK, Holl JL, Greenberg CC, Bilimoria KY.** 2020. Association between surgeon technical skills and patient outcomes. JAMA Surg **155:**960–968. https://doi.org/10.1001/jamasurg.2020.3007.
68. **Terner JM, Lomas LM, Smith ES, Barrett AC, Picker MJ.** 2003. Pharmacogenetic analysis of sex differences in opioid antinociception in rats. Pain **106:**381–391. https://doi.org/10.1016/j.pain.2003.08.008.
69. **Thompson AC, Kristal MB, Sallaj A, Acheson A, Martin LB, Martin T.** 2004. Analgesic efficacy of orally administered buprenorphine in rats: methodologic considerations. Comp Med **54:**293–300.
70. **Ueno H, Takahashi Y, Suemitsu S, Murakami S, Kitamura N, Wani K, Matsumoto Y, Okamoto M, Ishihara T.** 2020. Effects of repetitive gentle handling of male C57BL/6NCrl mice on comparative behavioural test results. Sci Rep **10:**3509. https://doi.org/10.1038/s41598-020-60530-4.
71. **van Dorp E, Yassen A, Sarton E, Romberg R, Olofsen E, Teppema L, Danhof M, Dahan A.** 2006. Naloxone reversal of buprenorphine-induced respiratory depression. Anesthesiology **105:**51–57. https://doi.org/10.1097/00000542-200607000-00012.
72. **Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE.** 1994. Clinical pharmacology of buprenorphine: Ceiling effects at high doses. Clin Pharmacol Ther **55:**569–580. https://doi.org/10.1038/clpt.1994.71.
73. **Yun M-H, Jeong S-W, Pai C-M, Kim S-O.** 2010. Pharmacokinetic-pharmacodynamic modeling of the analgesic effect of bupredermTM, in mice. Health **2:**824–831. https://doi.org/10.4236/health.2010.28124.
74. **Zoetis.** [Internet]. 2017. Simbadol (buprenorphine injection). [Cited 02 August 2022]. Available at: https://www2.zoetisus.com/content/pages/products/cats/SIMBADOL-Resources/documents/simbadol-prescribing-information.pdf.
75. **ZooPharm**. 2022. Buprenorphine SR-LAB. Swedesboro (NJ): ZooPharm Pharmaceuticals.
76. **ZooPharm Pharmaceuticals**. 2022. SR(TM) formulation characteristics. Swedesboro (NJ): ZooPharm Pharmaceuticals.