Analgesics in Small Mammals

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KEYWORDS

• Pain assessment • Analgesia • Analgesics • Rodents • Rabbits • Rat • Mouse • Guinea pig

KEY POINTS

- Effective use of analgesics in small mammals requires pain intensity to be assessed. After assessing the intensity of pain, an analgesic regimen can be formulated and administered and its efficacy confirmed by repeated pain assessment.
- Pain assessment tools are still in an early stage of development, but assessment of specific behaviors and use of grimace scales to assess facial expression can be used in many species.
- Analgesic dosage recommendations are based largely on clinical experience, but information is gradually accumulating based on objective assessment of efficacy in clinically relevant settings.

INTRODUCTION

Managing pain effectively in any species is challenging, but small mammals present some particular problems. This clinical review focuses on pain assessment and pain alleviation in rats, mice, guinea pigs, and rabbits, because there is a reasonable evidence base in these species on which to base clinical decisions. Suggestions are made as to how to extrapolate information to other species, such as gerbils, hamsters, degus, and chinchillas.

Although the underlying mechanisms of nociception and pain are similar in all mammals that present for veterinary treatment, detecting pain can be particularly difficult in rodents and rabbits. But if the presence of pain cannot be recognized and its intensity assessed, then analgesics cannot be used effectively. If pain fails to be detected, it may be considered there is no need to administer analgesics. If pain is suspected to be present but how much pain an animal is experiencing cannot be assessed, then the analgesic protocol cannot be adjusted to suit the need of each individual. If

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an analgesic is given, the reduction in pain must be able to be assessed to determine that the drug selected and the dose rate used have been effective in that individual animal.

Pain assessment in dogs and cats is not always straightforward, but most veterinary surgeons and veterinary technicians are familiar with the normal behavior of these species. The normal behavior and general appearance of small rodents, ferrets, and rabbits are often less well appreciated, so that signs associated with pain may be overlooked. In addition, several species of small mammals are nocturnal and may not be active when observed during normal working hours. They may also remain immobile in the presence of an observer if they perceive them as a threat. This can be a particular problem with rabbits and guinea pigs. Although it is not always easy to use behavior and changes in appearance to assess pain, it is important to overcome these difficulties so that pain can be prevented or controlled effectively in these small animals.

GENERAL SIGNS OF PAIN

As with dogs and cats, an initial assessment of a small mammal should be made without disturbing it. The animal's appearance and posture may be abnormal and it may appear hunched. Its coat may be unkempt and ruffled because of a lack of grooming and the presence of piloerection. Rats may have a blackish discharge around their eyes and nose, due to a build-up of secretions from their harderian glands. This build-up of material is a nonspecific response to ill health, pain, and other stress, but in the postoperative period it is a useful indicator that the animal could be in pain. While an animal is observed, it may demonstrate normal inquisitive behavior and explore its environment, but, as discussed previously, if it remains motionless this may be because it feels threatened rather than because it is in pain. If an animal has positioned itself in the back of its cage or pen or has hidden in bedding, this can also be a sign of fear but may also be due to pain.

Observing spontaneous behavior in a veterinary practice setting can be challenging—the smells, sounds, and sight of other patients, who may be predators of small mammals, may result in suppression of all behavior. If an area can be found that is free from both sounds and odors of predators, this helps assessment, and it is also now simple to set up remote observation of animals using a webcam or tethered camera system. Using a security-style camera with infrared sensitivity also allows observation during the dark phase of an animal's photoperiod, when many small mammals should be very active. Aside from allowing more reliable observations to be made, a quiet area away from predators reduces the stress associated with hospitalization and reduces the risk of stress-related problems, such as gastrointestinal disorders in rabbits and guinea pigs.

After observing an animal in as undisturbed state as possible, it should be approached and examined. When encouraged to move, the animal may have an abnormal gait or posture and may show uncharacteristic signs of aggression. Rats, mice, and gerbils usually rear when investigating what has disturbed them and the absence of this behavior may be due to pain. When handled, rather than attempting to evade capture, animals in pain may be apathetic or, as discussed previously, may be aggressive and bite the handler. When examining an animal, it may respond to manipulation or palpation of a painful area by vocalizing or trying to bite. Some mammals, such as guinea pigs, also vocalize loudly when not in pain and may respond to any manipulation by tensing their muscles and remaining immobile. Similar unresponsiveness can also be seen in rabbits. When examining small mammals, such

as mice, hamsters, and gerbils, use of a clear acrylic handling tube allows good observation, without the need for firm physical restraint (Fig. 1). This method of handling has also been shown to reduce stress and anxiety.[1,2]

SPECIFIC SIGNS OF PAIN

The changes, discussed previously, are nonspecific signs of pain. They can also occur as a result of general ill health but are nevertheless useful when other examinations suggest pain could be present, for example, due to otitis, dental disease, or arthritis. They can also be helpful when assessing animals after surgical procedures when some pain is inevitable unless particularly effective pain management strategies have been implemented.

The management of pain in dogs and cats has been greatly improved by the development of validated pain scales, incorporating behavioral changes that are reliable indicators of pain. In small mammals and rabbits, such scales are in a much earlier stage of development. Nevertheless, pain that has a visceral component, for example, after abdominal surgery or after orchidectomy, often produces some characteristic behaviors in rats, mice, rabbits, and guinea pigs.[3–7] Given the shared characteristics of these behaviors, it is probable that similar behaviors are also of value in assessing pain in other, less familiar species.

Rats, mice, rabbits, and guinea pigs may show contraction of the abdominal muscles, producing a hollowed-out appearance to the flanks (Figs. 2–4). Rats, mice, and rabbits may also press their abdomen to the ground (Fig. 5). Rats may arch their backs (Fig. 6) and rats, mice, and rabbits may stagger when performing normal behaviors. If a rat or mouse is in moderate or severe pain, these behaviors are seen frequently, for example, 4 to 5 abnormal behaviors in a 5-minute to 10-minute period. Rabbits show a similar frequency but may only do so if observed remotely. Even well-socialized rabbits, with a familiar observer, may reduce the incidence of these behaviors. Guinea pigs are even less demonstrative, and a prolonged period of observation, using remote monitoring, for 15 minutes to 30 minutes may be needed to identify these behavioral changes.[7] Achieving this in a busy veterinary practice may be impracticable, but other means of assessing pain, using facial expression (discussed later), may be more useful.

Anecdotally, rabbits with abdominal pain are said to grind their teeth, but this may not always be pain related. The author has also never observed this behavior in studies of pain related behavior in rabbits. Rabbits and all small mammals may stop eating and

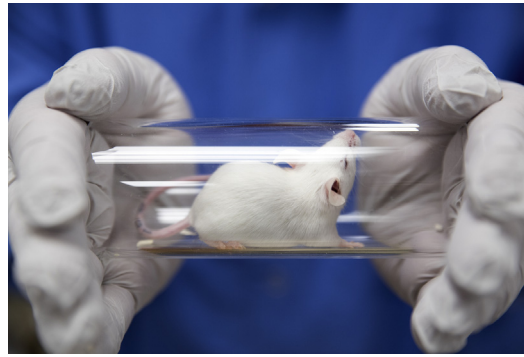

Fig. 1. Use of a handling tube to examine a mouse —the animal is encouraged to run into the tube while in its cage or transport box.

Fig. 2. Rabbit showing abdominal contraction due to pain after surgery (ovariohysterectomy) and insufficient analgesia. The animal is also showing some facial expression changes associated with pain (see **Fig. 12**).

drinking when experiencing pain. This can be difficult to detect because food is often provided as desired, but the consequent loss in body weight can easily be monitored.[8] This is one of the simplest ways of following an animal's progress after surgery or during treatment of any disease condition. A fall in food and water consumption caused by pain is a serious problem in small mammals, because failure to drink can rapidly lead to significant dehydration, and lack of food intake can predispose to the development of hypoglycemia in small mammals. In addition, in rabbits, guinea pigs, and chinchillas, disturbances in food intake can lead to the development of life-threatening gastrointestinal disturbances.

Rats and mice in pain reduce their performance of some highly motivated behaviors, such as burrowing and nest building. Measurement of these behaviors has been used to assess pain in carefully controlled studies,[9,10] and the approach could prove useful in a clinical setting. Mice in pain build less well-constructed nests and are slower to build a nest. Assessing nesting behavior before and after surgery might provide additional information as to the efficacy of analgesia. Digging behavior is less easy to assess in a home cage environment, but the methods used (filling a small bottle

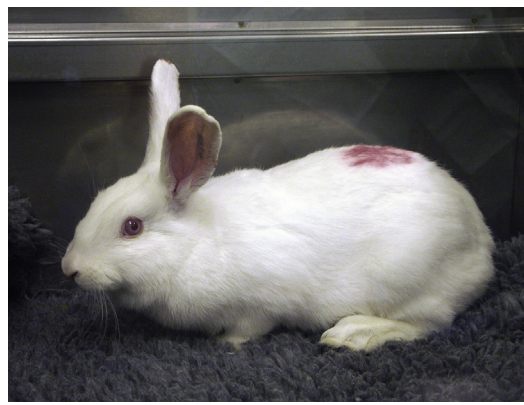

Fig. 3. Rabbit showing normal profile to the abdomen and normal posture after abdominal surgery with the provision of effective analgesia.

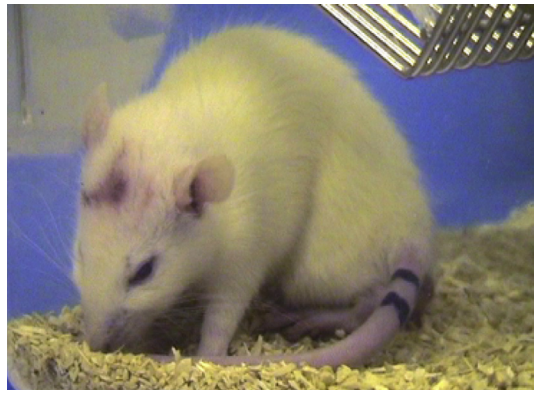

Fig. 4. Rat showing abdominal contraction and partial back arch due to postoperative abdominal pain.

with gravel or with diet pellets) is easy to implement.[11] This approach has been shown effective in detecting chronic inflammatory and neuropathic pain in rats so has the potential to be used to diagnose chronic painful conditions. Demonstrating an increase in burrowing after administration of an analgesic confirms the presence of pain and allows monitoring of analgesic efficacy.

RODENT AND RABBIT GRIMACE SCALES (PAIN FACES)

Most pet owners and many veterinarians consider they can assess the emotional state of an animal from its facial expressions. Charles Darwin considered facial expressions as indicating a range of emotions and noted that similar expressions were shared across different species and between animals and humans.[12] Applying this approach in an objective way to assess pain is a recent development.[13] After the initial demonstration that mice show characteristic pain faces that could be used to develop a mouse grimace scale (**Figs. 7** and **8**), similar scales have been developed in other species. Rats have been shown to have facial expressions characteristic of pain[14] (**Figs. 9** and **10**) as have rabbits[15] (**Figs. 11–13**). Grimace scales have also been developed in horses,[16] sheep and lambs,[17,18] and pigs,[19] and similar approaches may be applicable in a wide range of species.[20]

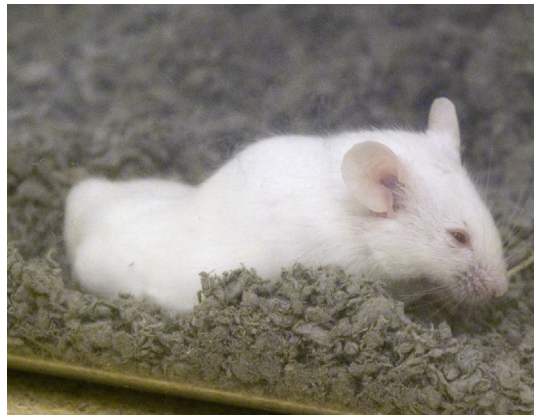

Fig. 5. Mouse showing a characteristic press due to postsurgical abdominal pain.

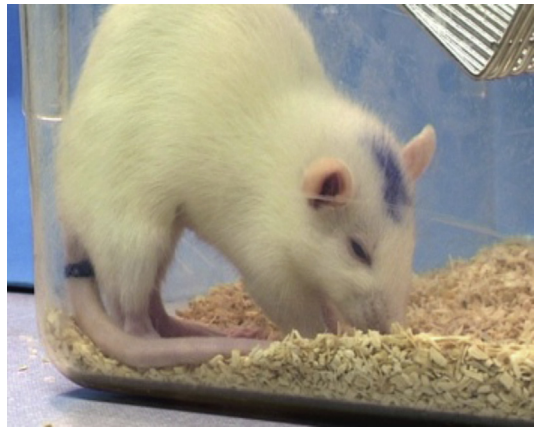

Fig. 6. Back arching caused by abdominal pain after laparotomy in the rat.

The expressions shown can be used to evaluate the degree of pain but care must be taken because other factors can also result in animals showing these facial expressions.[21] An attraction of using grimace scales is that similar changes seem to occur with different types and sources of pain and can be easily captured by both direct observations and use of video and still images. This approach is still at an early stage of development, but initial studies suggest it can be used as a cage-side means of assessing pain.[22,23] Facial expression may also be less susceptible to changing as a result of the nonspecific effects of analgesics. This can be a problem when using other behavioral assessments—for example, opioids can either increase activity (in mice and gerbils) or cause sedation (in rats and rabbits). Using grimace scales in combination with the other indicators, described previously, may provide the best means of assessing pain in many species, not only small mammals.

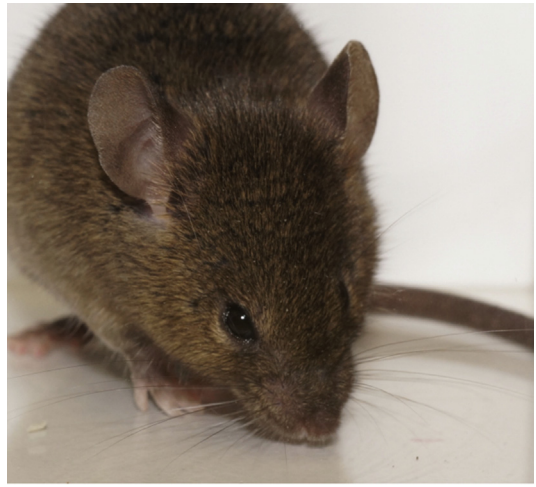

Fig. 7. Normal facial expression in the mouse.

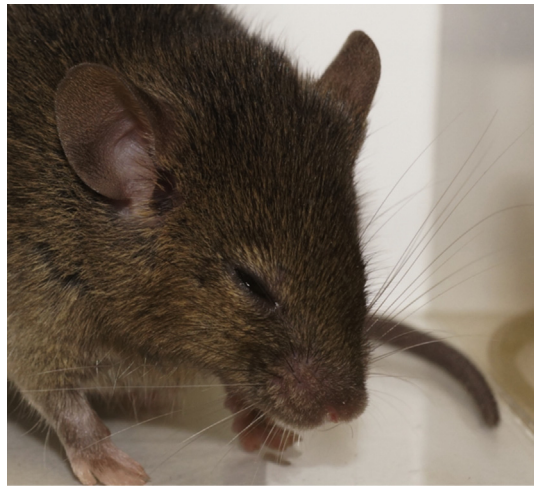

Fig. 8. Pain face in the mouse—showing nose bulging, orbital tightening, and cheek bulge.

ASSESSING PAIN IN CLINICAL PRACTICE

As experience is gained in observing the normal behavior patterns of small mammals and rabbits, changes in the frequency of normal behaviors and the occurrence of abnormal behaviors are detected with greater confidence. Although specific signs of pain, such as guarding of an injured area, may be seen, many of the signs are nonspecific and can also occur in response to nonpainful conditions. It is, therefore, important to consider the appearance of the animal in relation to its case history and other clinical findings. It is also important to appreciate that pain assessment

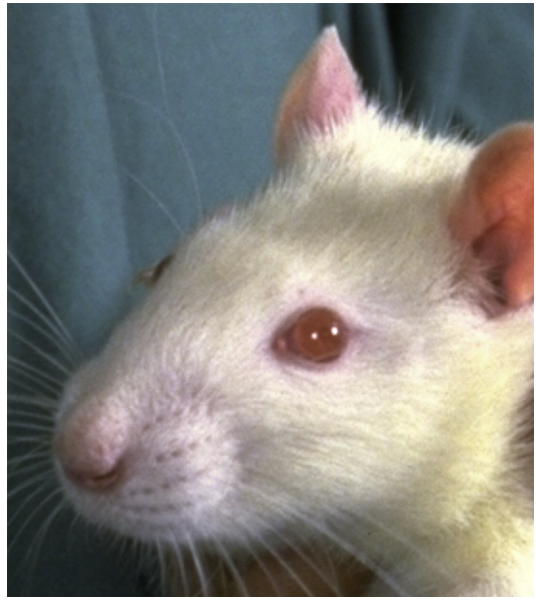

Fig. 9. Normal facial expression in the rat.

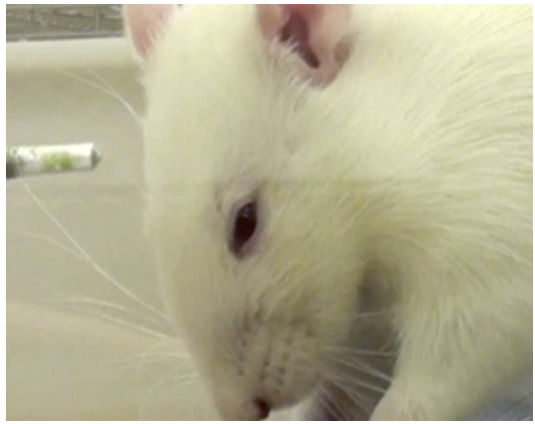

Fig. 10. Pain face in the rat—showing ear changes, orbital tightening, and clumping of whiskers.

takes time—observing specific abnormal behaviors takes 5 minutes to 10 minutes per animal to allow effective assessments. Observing general behavior and activity takes even longer. Couple this with the relative lack of familiarity veterinarians have, and it is clear that one of the best people to assess pain in a companion animal is the owner. Encouraging owners of animals to make detailed assessments, especially in combination with administration of therapy, may be a valuable adjunct to assessments in the clinic.

PAIN PREVENTION AND ALLEVIATION

Postoperative and Posttrauma Pain

Effective pain relief after surgery should be considered part of an integrated approach to perioperative care. There is extensive evidence in people that stress and anxiety increase the degree of pain experienced and increase the need for pain relief. In addition, veterinarians should be concerned to alleviate both distress and discomfort as well as pain. Postoperative pain relief is important in all small mammals, but providing

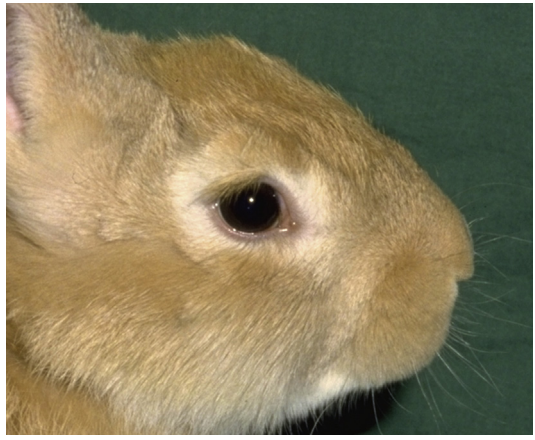

Fig. 11. Normal facial expression in the rabbit.

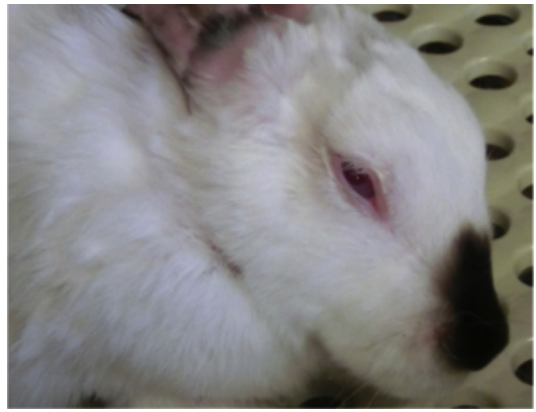

Fig. 12. Pain face in the rabbit—showing marked orbital tightening.

pain relief in rabbits and guinea pigs is especially important to ensure an uncomplicated recovery from surgery. As in other species, the most obvious means of preventing pain is by administration of analgesic drugs; however, the choice of drug and the timing of its administration should be considered carefully. It is also important not to overlook other important factors, for example, careful surgical technique with gentle handling of tissues reduces the degree of postoperative pain. Analgesic use should also be combined with nutritional and fluid and support and general nursing care. These considerations apply to all species, but in small mammals several particular issues need greater attention.[24] Small mammals are particularly susceptible to developing hypothermia during anesthesia. Most anesthetic protocols include provision of warming, but this must be continued into the postoperative period. A suitable recovery area should be established as part of the preoperative preparations, so that it can be stabilized at an appropriate temperature. Initially a temperature of approximately 35°C should be maintained and this can be lowered to 26°C to 28°C as the animal recovers consciousness. Animals should be provided with warm, comfortable bedding. A layer of synthetic fleece should be provided for the initial recovery period, but once

Fig. 13. Pain face in the rabbit—showing folding and flattening of the ears and orbital tightening.

the animal has regained activity it can be transferred to a cage or pen containing its normal bedding and nesting material. Rabbits and guinea pigs should be provided with good quality hay or straw. This type of bedding allows the animal to surround itself with insulating material, which provides both warmth and a sense of security. It also encourages them to eat as soon as possible, so helping prevent development of gastrointestinal disturbances.

Water should be provided, but care must be taken that this does not spill, because if the animal becomes wet it loses heat rapidly. Small rodents are usually used to using sipper bottles, as are rabbits, so this is not usually a problem, but it can present difficulties if a bowl is used for rabbits and guinea pigs. Even after uncomplicated anesthesia and surgery and with good analgesia, fluid intake may be reduced, so routine administration of warmed (37°C) subcutaneous or intraperitoneal dextrose/saline at the end of surgery is advisable.

Provided an animal has recovered well from anesthesia, it is probably best returned home to a familiar environment. The owner should be advised to observe the animal closely for the next few days, to be sure it is eating and drinking and passing feces. Establishing effective analgesia before discharging from the clinical helps ensure the animal recovers well.

Analgesic Agents

As in other species, a range of different analgesics is available, including nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and local anesthetics. Information concerning appropriate dose rates has been drawn from a variety of sources. Some species of small mammals have been used in laboratory evaluations of the safety and efficacy of analgesic agents. Extensive data of this type are available for rats and mice, but there is less information concerning rabbits, guinea pigs, hamsters, and gerbils. There are no data of this type for the less common small mammals, such as chinchillas and chipmunks. The information provided by laboratory studies is useful and provides information of safety and efficacy, in particular analgesic tests. The tests are not always directly relevant to the types of pain seen in veterinary practice, however, so dose rates need to be estimated carefully. It is also important to note that these studies were carried out in healthy laboratory animals, in controlled environmental conditions. Administration of analgesics to animals in poor health or use of analgesics concurrently with other medication may markedly alter an individual's response. Unfortunately, there are few studies of the efficacy of analgesics in clinically relevant situations. The majority of information has, therefore, been obtained from clinical experience. Dose rates are often recommended based on dose rates initially estimated by extrapolation from other species. When applied in clinical situations and found to be at least safe, these dose rates become established in textbooks and review articles,[25] even if efficacy has not been evaluated reliably. It is, therefore, important to continue to review analgesic use because recommendations change more frequently than for the more familiar companion animal species.

Fortunately, clinical experience suggests that the analgesics that are frequently used in dogs and cats can all be used safely for the control of postoperative pain in small mammals and rabbits. Although none of the agents listed in **Table 1** has manufacturer recommendations for small mammals, many are extensively used both in clinical practice and in laboratory animals.

Nonsteroidal anti-inflammatory drugs

Although it is likely that all the agents currently available for use in companion animals can be used safely in small mammals and rabbits, most published data are available

Table 1
Analgesics for use in small mammals. Suggested dose rates based on clinical experience of the author and other colleagues. None of these agents has manufacturer recommendations for use in these species. Effects vary in individual animals, and each animal should be assessed to try to determine the efficacy of the analgesic

Analgesic	Gerbil and Hamster	Guinea Pig	Mouse	Rat	Rabbit
Buprenorphine	0.1 mg/kg sc, ?6–8 hourly	0.05 mg/kg sc, 6–12 hourly	0.1 mg/kg sc, 4–8 hourly	0.05 mg/kg sc, 4–8 hourly	0.01–0.05 mg/kg sc or IV, 6–12 hourly
Butorphanol	?	2 mg/kg sc, 2 hourly	1–5 mg/kg sc, 2 hourly	2 mg/kg sc, 2 hourly	0.1–0.5 mg/kg sc or IV, 2 hourly
Carprofen	5 mg/kg sc, ? daily	4 mg/kg sc, ? daily	5 mg/kg sc, bid	5 mg/kg sc or orally, daily	1.5 mg/kg po, 4 mg/kg sc or IV
Meloxicam	?	0.5–1.0 mg/kg sc or orally, ? daily	5 mg/kg sc or orally, bid	1 mg/kg sc or orally, ? daily	0.4–0.6 mg/kg po, 0.4–0.6 mg/kg sc, ? daily
Morphine	?	2–5 mg/kg sc or IM, 4 hourly	5 mg/kg sc or IM, 4 hourly	2.5 mg/kg sc or IM, 4 hourly	2 mg/kg sc, IM, 3–4 hourly
Meperidine	?	10–20 mg/kg sc or IM, 2–3 hourly	10–20 mg/kg sc or IM, 2–3 hourly	10–20 mg/kg sc or IM, 2–3 hourly	?
Tramadol	?	?	5 mg/kg sc, IP or po	5 mg/kg sc, IP or po	?

?, insufficient data to recommend dose rates.
Abbreviations: bid, twice a day; IM, intramuscularly; IP, interperitoneal; po, per os (by mouth); sc, subcutaneous.
Data from Flecknell and Waterman-Pearson, 2000, "Pain management in animals", Flecknell, "Laboratory animal anaesthesia, 2015, clinical experience.

for meloxicam and carprofen. There seems some marked species variation in efficacy of NSAIDs, with very high dose rates required in mice (20 mg/kg) in comparison with rats (1 mg/kg) for postoperative analgesia.[26–28] Similarly in rabbits, high doses of meloxicam are needed for postoperative analgesia, and these need to be combined with local anesthesia or opioids for effective pain relief,[6,29,30] illustrating the care needed when extrapolating between species, without the means of evaluating clinical efficacy.

Some NSAIDs have been associated with undesirable side effects. Although ketoprofen has effective in rats,[31] it has been reported to cause gastrointestinal ulceration.[32,33] There are anecdotal reports of toxicity of carprofen and meloxicam, but such reports are uncommon and the short treatment period required for postoperative pain management is unlikely to result in undesirable side effects. Dosing recommendations for carprofen and meloxicam are usually once daily, but this is based on few data, and twice-daily administration may be required in mice.[34,35] In the rabbit, once-daily administration of meloxicam may be sufficient.[36] In the guinea pig, meloxicam combined with local anesthetic block at the surgical site provided effective pain relief.[7]

Meloxicam is one of the most widely used NSAIDs in small mammals and rabbits in veterinary clinical practice because it is available as both an injectable and palatable oral formulation. The oral formulation is easy to administer to a range of species so can be given to owners to continue analgesic treatment at home.

Acetaminophen (Paracetamol)

Although there are extensive data demonstrating the efficacy of acetaminophen in models of nociception,[37] results when using this agent for postsurgical pain relief have been disappointing (Roughan, personal communication, 2010).[28,38] It is possible that combinations of acetaminophen with NSAIDs or weak opioids may be more effective, but so far few controlled studies have been undertaken for postoperative pain. One attraction of acetaminophen is its availability in a palatable solution,[39] but given its apparent poor efficacy, even at high dose rates, it is usually preferable to administer an NSAID, such as meloxicam.

Opioids

Although there are extensive data on use of a wide range of opioids in rats and mice, the most extensively used agent in these species, and in other small mammals, is buprenorphine.[40] Although this agent is a partial agonist, the degree of analgesia provided is often sufficient to control most postsurgical pain. The duration of action is dose dependent,[41] with higher dose rates providing a longer effect. When administered at the most commonly recommended dose rates (as in **Table 1**), the duration of action may range from 4 hours to 8 hours, depending on the species and the individual.[42–44] This is considerably longer than other opioids, such as morphine, and this prolonged action is largely responsible for the popularity of this agent.

An uncommon side effect of buprenorphine in rats is the onset of pica, which usually manifests as compulsive eating of bedding.[45] This is a nonspecific opioid effect, thought to indicate nausea.[46] If it occurs, then further use of opioids should be avoided in the patient.

Recently a slow-release formulation has become available in the United States, which provides sustained plasma concentrations of buprenorphine for 3 days.[47–49] The slow-release formulation has been shown to have efficacy in several different situations and it may offer an effective means of managing pain, especially when animals are to return home with their owners. One concern is that repeated dosing with

buprenorphine for several days has been associated with detrimental effects. This does not seem to occur with slow-release formulations,[43] perhaps because plasma concentrations of the agent are more stable, in contrast to the repeated peaks and troughs associated with intermittent dosing. At present, most data are available for use in rats and mice, but information on pharmacokinetics in other species is being produced.[48] Although many surgical procedures do not result in pain of sufficient intensity and duration to warrant 3 days of opioid administration, if the slow-release formulation can be used without causing undesirable side effects, then it provides a valuable addition to options for pain management in all species.

There is less information on the relative efficacy of other opioids, such as oxymorphone, hydromorphone, butorphanol, and morphine, when used to manage pain in a clinical setting. Laboratory data indicate these opioids are all effective analgesics in rats.[50] They have a shorter duration of action, however, than buprenorphine in small mammals[42] so if used, either frequent repeated dosing is required or analgesia provided using other agents.

Patch formulations of opioids have been used in rabbits, with reports indicating that effective plasma concentrations could be produced, but this was complicated by rapid hair regrowth. Using depilating agents resulted in rapid fentanyl absorption and signs of sedation[51] but with no demonstration of efficacy. Although newer designs of patch can be cut into small pieces to reduce the dose applied, there are no controlled studies of efficacy in small rodent.

Opioids can also be administered epidurally or intrathecally, by percutaneous injection, as in cats and dogs. The technique in rabbits, guinea pigs, and rats is reasonably practicable,[52] although a recent evaluation of intrathecal morphine in rats showed that, unlike in dogs and cats, the duration of action of this opioid was not prolonged when administered by this route.[53] Effective analgesia was, however, produced with a much reduced dose of morphine.

Opioid side effects in small mammals and rabbits rarely cause clinically significant problems. Concern has been expressed that the reduction in gut motility by opioids could be a problem in rabbits, guinea pigs, and chinchillas, because of the sensitivity of these species to postoperative ileus. This does not seem to be a problem in clinical practice. Any effects of opioid administration are likely to be minimal compared with the effects of surgery in producing ileus. In addition, provision of effective pain relief encourages the animals to resume feeding rapidly, and this helps re-establish normal gut function. Finally, if there are concerns about ileus, prokinetics, such as cisapride, can be administered. As an alternative, the H_2 blocker ranitidine has prokinetic properties in rabbits and is often more readily available than cisapride.[54]

Tramadol

Tramadol is a weak opioid with additional analgesic actions by inhibition of serotonin and noradrenaline reuptake, enhancing descending inhibition of nociceptive pathways.[55] The pharmacokinetics of this agent have been studied in rats, mice, and rabbits and efficacy in laboratory models of nociception demonstrated.[56] Studies of its efficacy for postoperative pain management in rats and mice have shown variable efficacy,[57–59] but its good oral bioavailability makes it a potentially useful agent for postoperative analgesia.

Tramadol undergoes rapid metabolism in many species, to a range of metabolites, many of which have analgesic activity. In the rat, the main metabolite is a more potent opioid than tramadol itself.[60] In the rabbit, plasma concentrations of tramadol were low after oral administration[61] and doses recommended for analgesic use (4.4 mg/kg intravenous [IV]) had minimal effects on isoflurane mac.[62] Until clinical

efficacy is demonstrated in rabbits, it should be used only when other agents are considered unsuitable.

Because tramadol is available as an oral formulation, it may be suitable for prescribing to provide more prolonged analgesia in animals once they return home, perhaps in combination with an NSAID when more potent analgesia is required.

Local anesthetics

The use of local anesthetics in small mammals has been a neglected option for the provision of postoperative analgesia. This may be due to misinterpretation of some early studies, resulting in statements in textbooks that these agents were highly toxic in rodents. This is clearly not the case. The toxic doses in small rodents, for all the commonly used local anesthetics is similar to that in other species. There are fewer data in rabbits and guinea pigs, but clinical experience and laboratory studies indicate the agents can all be used safely and effectively.

As in other larger species, local anesthetics can be administered as splash blocks, by local infiltration, by blocking specific sensory nerves, and by the epidural or intrathecal route. When using these agents in small mammals, the total safe dosage should be calculated and prepared for use. Although the agents are no more toxic than in other species, the total dose in a 30-g mouse is small (eg, 0.03 mL of 1% lidocaine). When infiltrating a large surgical field (eg, after radical mastectomy in a rat), it is easy to inadvertently overdose. The volume of agent can be increased by dilution, but this reduces the duration of action. Dilutions of lidocaine to 0.25% have been shown to provide effective local block.[63] Lidocaine can also be combined with bupivacaine to provide rapid onset block, followed by prolonged block due to the action of the bupivacaine. Although this approach results in a reduced duration of action of bupivacaine,[64] it is often of considerable clinical benefit by providing effective immediate pain relief. The toxicity of these agents is additive, and in rabbits the recommended maximum dose rates for cats seem appropriate (eg, 1 mg/kg of each agent). In small rodents, higher doses have proved safe and effective in the author's experience (10-mg/kg lidocaine plus 5-mg/kg bupivacaine). Dilution of bupivacaine 1:4 has only a moderate effect on duration of action, so combining the 2 agents in a 50:50 mix and adding an equal volume of water for injection usually provides sufficient volume for infiltration.

Local anesthetic creams, applied topically, are useful for preventing pain during venipuncture[65] and in rabbits provide full-thickness analgesia when applied to the ear.[15]

Preventive Analgesia

Use of preventive analgesia is widely recommended in larger species and the same approach can be used in small mammals. In addition to ensuring pain alleviation is effective in the immediate recovery period, administration of an opioid analgesic as preanesthetic medication potentiates the effects of the anesthetic agents that are administered. This enables effective surgical anesthesia using dose rates of anesthetic that are less depressant to body systems. If volatile agents, such as isoflurane and sevoflurane, are used, then it is easy to adjust the maintenance concentration of anesthetic to allow for this effect. For example, if buprenorphine has been administered 30 minutes to 60 minutes before induction of anesthesia, the maintenance concentration of isoflurane is reduced by approximately 0.5% and sevoflurane by 1%. The induction concentration does not need to be adjusted. Although the time taken to reach a surgical plane of anesthesia is shorter after administration of opioids, this effect is rarely noted in practice. Recovery is not affected but may be smoother because the animal is not experiencing postsurgical pain. It is more difficult to assess the effect

when using injectable anesthetic formulations, but in rabbits, there are reports of the use of mixtures of ketamine/medetomidine and either butorphanol or buprenorphine.[66,67] Although these combinations seem safe and effective, the effects are primarily to prolong the duration of anesthesia, and the anesthetic dose sparing effects seen in other species (eg, cats) are not as apparent.

Preoperative administration of NSAIDs does not influence anesthetic depth but can result in more effective postoperative analgesia when administered prior to surgery. One concern is the potentially high incidence of chronic renal disease in small mammals, in particular rabbits and guinea pigs, and especially in older animals. Because preanesthetic assessment of renal function may not be undertaken, it may be safer to delay administration of the NSAID until the end of surgery, during recovery from anesthesia, in animals considered at risk.

Outpatient Analgesia

Although several agents are available that should, when administered at appropriate doses, provide effective analgesia, it can be challenging to extend the period of pain relief if an animal is to be returned home. Returning to the home environment may be beneficial in reducing stress caused by unfamiliar odors, sounds, and noises. It is also important, however, that effective pain relief is provided when necessary. One potentially attractive option is the addition of analgesics to the drinking water, and there are several reports of this approach in a laboratory setting.[68,69] There are several significant problems in using this approach. Small rodents are nocturnal, so little water, and hence little analgesic, is consumed during the day. If the degree of pain relief is ineffective at the end of the day, then animals have a reduced fluid intake. Addition of the analgesic may make the water unpalatable. Rats and guinea pigs are also neophobic, so even if the material is palatable, they may not consume it unless they have been familiarized to the taste previously. Finally, the volume of fluid consumed by small rodents and rabbits varies very considerably between individuals, so the dose of analgesic received also is highly variable. In summary, it is better to provide the owners with a syringe and a small quantity of oral medication, such as meloxicam.

Recommendations

Although it is always important to exercise clinical judgment as to which analgesic regimen is likely to be effective for a particular patient, some general guidance can be suggested. Whichever regimen is selected, it is important to attempt to assess pain to evaluate the efficacy of the analgesics administered.

A typical regimen that is likely to provide effective analgesia after ovariohysterectomy or similar surgery in rabbits or mammary tumor removal in rats is buprenorphine preoperatively, meloxicam or carprofen during recovery from anesthesia, and followed by repeated doses of the NSAID by mouth for the following 1 day to 2 days.[30] If needed, the buprenorphine dosing could be repeated 5 hours to 7 hours after recovery. If prolonged moderate or severe pain is anticipated, then slow-release buprenorphine may be advantageous. Procedures, such as orchiectomy, may not require such prolonged treatment, and use of an opioid together with a single dose of an NSAID might be sufficient. As discussed previously, adding a local anesthetic block seems particularly effective during procedures, such as orchiectomy, where infiltration of the surgical site is easy. To provide both immediate local anesthetic effects, and some postsurgical analgesia, lidocaine should be combined with bupivacaine (or other longer acting local anesthetic).

Managing Other Causes of Pain

Chronic pain may arise from conditions, such as neoplasia, arthritis, and dental disease. Older rodents, in particular rats, commonly develop arthritis, and this may markedly affect their quality of life. Dental disease is also common in rabbits and guinea pigs. Although malocclusion of molar and premolar teeth can be treated surgically, this is a major procedure and may be considered undesirable in specific cases. In these circumstances, control of the associated pain by oral administration of NSAIDs, such as meloxicam, coupled with more conservative dentistry may enable the animal to continue to lead a comfortable life or allow its general clinical condition to be improved before anesthesia and surgery.

As discussed previously, some data exist concerning safety of analgesics in these species, but these assessments are invariably carried out in otherwise healthy, young adult animals. Care, therefore, should be taken when extrapolating these findings to animals that may have preexisting organ damage—for example, chronic renal disease is common in older hamsters, rats, and guinea pigs. This is rarely a significant clinical problem when drugs are used acutely to control postsurgical pain, but special care should be taken if analgesics are administered longer term to manage chronic painful conditions, such as arthritis. Despite these concerns, in the author's experience, oral administration of low doses of NSAIDs for long periods can have positive effects in arthritic rodents. A regimen of 2 weeks to 3 weeks of treatment, followed by a 7-day break, followed by resumption of treatment, reduces the risk of undesirable side effects. Other means of reducing arthritic pain should not be overlooked—feeding of a soft mash, rather than a hard, pelleted diet can improve food intake, especially if arthritis of the mandibular joint is present. Provision of additional soft bedding is also advisable. In addition, consider the design and location of any water bottles, and change these if they require the animal to adopt a posture that could exacerbate joint pain. Anecdotal reports are available regarding the safety of long-term administration of NSAIDs, and it seems that meloxicam can be administered to rabbits for weeks or months at low doses (0.2 mg/kg once a day or twice a day orally) to provide sufficient pain relief to allow animals with dental problems to continue to eat.[70] Adjunctive therapies for arthritis that may be of benefit in other species may also be effective in small mammals. For example, glucosamine/chondroitin has been used in rabbits, with dose rates extrapolated from the cat, and laboratory studies indicate a beneficial effect of glucosamine.[71]

Pain may also arise due to other medical conditions, such as otitis externa, ocular disease, abscesses, and trauma. As in other species, pain should be managed effectively as part of the treatment plan for the condition. Regrettably, analgesic administration may be an afterthought, or completely neglected, when managing conditions where medical treatment is likely to resolve the problem reasonably rapidly. Use of analgesics should always be considered—particularly before undertaking procedures that are likely to exacerbate the degree of pain. For example, administration of an NSAID or even an opioid before attempting to apply topical treatment to otitis externa in a rabbit can be of considerable benefit to the patient.

SUMMARY

Pain in small mammals and rabbits can be managed as effectively as in other species. A range of potentially effective agents is available, and safe dose rates have been established for mice, rats, rabbits, and guinea pigs. Although less information is available of other species, extrapolation between related species often enables safe

dosing of less familiar small mammals. New techniques for pain assessment enable evaluation of the efficacy of an analgesic regimen in individual animals, although this remains challenging in a clinical setting.

REFERENCES

1. Gouveia K, Hurst JL. Reducing mouse anxiety during handling: effect of experience with handling tunnels. PLoS One 2013;8(6):e66401. Mintz EM, ed.
2. Hurst JL, West RS. Taming anxiety in laboratory mice. Nat Methods 2010;7(10):825–6.
3. Roughan JV, Flecknell PA. Behaviour-based assessment of the duration of laparotomy-induced abdominal pain and the analgesic effects of carprofen and buprenorphine in rats. Behav Pharmacol 2004;15(7):461.
4. Wright-Williams S, Flecknell PA, Roughan JV. Comparative effects of vasectomy surgery and buprenorphine treatment on faecal corticosterone concentrations and behaviour assessed by manual and automated analysis methods in C57 and C3H mice. PLoS One 2013;8(9):e75948. Price TJ, ed.
5. Leach MC, Allweiler S, Richardson C, et al. Identifying potential behavioural indicators of pain in rabbits following ovariohysterectomy - preliminary study. Animal Technology and Welfare 2009;8(2):49–52, 70, 74, 78, 82.
6. Leach MC, Allweiler S, Richardson C, et al. Behavioural effects of ovariohysterectomy and oral administration of meloxicam in laboratory housed rabbits. Res Vet Sci 2009;87(2):336–47.
7. Ellen Y, Flecknell P, Leach M. Evaluation of using behavioural changes to assess post-operative pain in the Guinea pig (Cavia porcellus). PLoS One 2016;11(9):e0161941. Pritchett-Corning KR, ed.
8. Liles JH, Flecknell PA. A comparison of the effects of buprenorphine, carprofen and flunixin following laparotomy in rats. J Vet Pharmacol Ther 1994;17(4):284–90.
9. Arras M, Rettich A, Cinelli P, et al. Assessment of post-laparotomy pain in laboratory mice by telemetric recording of heart rate and heart rate variability. BMC Vet Res 2007;3(1):16.
10. Andrews N, Legg E, Lisak D, et al. Spontaneous burrowing behaviour in the rat is reduced by peripheral nerve injury or inflammation associated pain. Eur J Pain 2012;16(4):485–95.
11. Jirkof P. Burrowing and nest building behavior as indicators of well-being in mice. J Neurosci Methods 2014;234:139–46.
12. Darwin C. The expression of emotion in man and animals. London: Penguin; 2009.
13. Langford DJ, Bailey AL, Chanda ML, et al. Coding of facial expressions of pain in the laboratory mouse. Nat Methods 2010;7(6):447–9.
14. Sotocinal SG, Sorge RE, Zaloum A, et al. The rat grimace scale: a partially automated method for quantifying pain in the laboratory rat via facial expressions. Mol Pain 2011;7(1):55.
15. Keating SCJ, Thomas AA, Flecknell PA, et al. Evaluation of EMLA cream for preventing pain during tattooing of rabbits: changes in physiological, behavioural and facial expression responses. PLoS One 2012;7(9):e44437.
16. Costa ED, Minero M, Lebelt D, et al. Development of the horse grimace scale (HGS) as a pain assessment tool in horses undergoing routine castration. PLoS One 2014;9(3):e92281. Hillman E, ed.

17. McLennan KM, Rebelo CJB, Corke MJ, et al. Development of a facial expression scale using footrot and mastitis as models of pain in sheep. Appl Anim Behav Sci 2016;176:19–26.
18. Guesgen MJ, Beausoleil NJ, Leach M, et al. Coding and quantification of a facial expression for pain in lambs. Behav Processes 2016;132:49–56.
19. Di Giminiani P, Brierley VLMH, Scollo A, et al. The assessment of facial expressions in piglets undergoing tail docking and castration: toward the development of the piglet grimace scale. Front Vet Sci 2016;3:261.
20. Descovich KA, Wathan J, Leach MC, et al. Facial expression: an under-utilised tool for the assessment of welfare in mammals. ALTEX 2017;34(3):409–29.
21. Defensor EB, Corley MJ, Blanchard RJ, et al. Facial expressions of mice in aggressive and fearful contexts. Physiol Behav 2012;107(5):680–5.
22. Oliver V, De Rantere D, Ritchie R, et al. Psychometric assessment of the rat grimace scale and development of an analgesic intervention score. PLoS One 2014;9(5):e97882. McCormick C, ed.
23. Leung V, Zhang E, Pang DS. Real-time application of the rat grimace Scale as a welfare refinement in laboratory rats. Sci Rep 2016;6(1):31667.
24. Flecknell P. Laboratory animal anaesthesia. London: Academic Press; 2015.
25. Hawkins MG. The use of analgesics in birds, reptiles, and small exotic mammals. Journal of exotic pet medicine 2006;15(3):177–92.
26. Wright-Willams S, Courade J, Richardson C, et al. Effects of vasectomy surgery and meloxicam treatment on faecal corticosterone levels and behaviour in two strains of laboratory mouse. Pain 2007;130(1–2):108–18.
27. Miller AL, Roughan JV. A comparison of abdominal and scrotal approach methods of vasectomy and the influence of analgesic treatment in laboratory mice. Lab Anim 2012;46(4):304–10.
28. Matsumiya LC, Sorge RE, Sotocinal SG, et al. Using the mouse grimace scale to reevaluate the efficacy of postoperative analgesics in laboratory mice. J Am Assoc Lab Anim Sci 2012;51(1):42–9.
29. Cooper CS, Metcalf-Pate KA, Barat CE, et al. Comparison of side effects between buprenorphine and meloxicam used postoperatively in Dutch belted rabbits (Oryctolagus cuniculus). J Am Assoc Lab Anim Sci 2009;48(3):279–85.
30. Goldschlager GB, Gillespie VL, Palme R, et al. Effects of multimodal analgesia with lowdose buprenorphine and meloxicam on fecal glucocorticoid metabolites after surgery in New Zealand white rabbits (Oryctolagus cuniculus). J Am Assoc Lab Anim Sci 2013;52(5):571–6.
31. Roughan JV, Flecknell PA. Behavioural effects of laparotomy and analgesic effects of ketoprofen and carprofen in rats. Pain 2001;90(1):65–74.
32. Lamon TK, Browder EJ, Sohrabji F, et al. Adverse effects of incorporating ketoprofen into established rodent studies. J Am Assoc Lab Anim Sci 2008;47(4):20–4.
33. Shientag LJ, Wheeler SM, Garlick DS, et al. A therapeutic dose of ketoprofen causes acute gastrointestinal bleeding, erosions, and ulcers in rats. J Am Assoc Lab Anim Sci 2012;51(6):832–41.
34. Engelhardt G, Homma D, Schlegel K, et al. General pharmacology of meloxicam-part I: effects on CNS, gastric emptying, intestinal transport, water, electrolyte and creatinine excretion. Gen Pharmacol 1996;27(4):673–7. Available at: http://www.sciencedirect.com/science/article/pii/0306362395020349.
35. Busch U, Schmid J, Heinzel G, et al. Pharmacokinetics of meloxicam in animals and the relevance to humans. Drug Metab Dispos 1998;26(6):576–84. Available at: http://dmd.aspetjournals.org/content/26/6/576.short.

36. Turner PV, Chen HC, Taylor WM. Pharmacokinetics of meloxicam in rabbits after single and repeat oral dosing. Comp Med 2006;56(1):63–7. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=16521861&retmode=ref&cmd=prlinks.
37. Miranda HF, Puig MM, Prieto JC, et al. Synergism between paracetamol and nonsteroidal anti-inflammatory drugs in experimental acute pain. Pain 2006;121(1–2):22–8.
38. Dickinson AL, Leach MC, Flecknell PA. The analgesic effects of oral paracetamol in two strains of mice undergoing vasectomy. Lab Anim 2009;43(4):357–61.
39. Fleischmann T, Arras M, Sauer M, et al. Voluntary intake of paracetamol-enriched drinking water and its influence on the success of embryo transfer in mice. Res Vet Sci 2017;111:85–92.
40. Stokes EL, Flecknell PA, Richardson CA. Reported analgesic and anaesthetic administration to rodents undergoing experimental surgical procedures. Lab Anim 2009;43(2):149–54.
41. Roughan JV, Flecknell PA. Buprenorphine: a reappraisal of its antinociceptive effects and therapeutic use in alleviating post-operative pain in animals. Lab Anim 2002;36(3):322–43.
42. Gades NM, Danneman PJ, Wixson SK, et al. The magnitude and duration of the analgesic effect of morphine, butorphanol, and buprenorphine in rats and mice. Contemp Top Lab Anim Sci 2000;39(2):8–13.
43. Jirkof P, Tourvieille A, Cinelli P, et al. Buprenorphine for pain relief in mice: repeated injections vs sustained-release depot formulation. Lab Anim 2015;49(3):177–87.
44. Sauer M, Fleischmann T, Lipiski M, et al. Buprenorphine via drinking water and combined oral-injection protocols for pain relief in mice. Appl Anim Behav Sci 2016;185:103–12.
45. Clark JA, Myers PH, Goelz MF, et al. Pica behavior associated with buprenorphine administration in the rat. Lab Anim Sci 1997;47(3):300–3.
46. Batra VR, Schrott LM. Acute oxycodone induces the pro-emetic pica response in rats. J Pharmacol Exp Ther 2011;339(3):738–45.
47. Kendall LV, Wegenast DJ, Smith BJ, et al. Efficacy of sustained-release buprenorphine in an experimental laparotomy model in female mice. J Am Assoc Lab Anim Sci 2016;55(1):66–73.
48. DiVincenti L, Meirelles LAD, Westcott RA. Safety and clinical effectiveness of a compounded sustained-release formulation of buprenorphine for postoperative analgesia in New Zealand white rabbits. J Am Vet Med Assoc 2016;248(7):795–801.
49. Foley PL. Evaluation of a sustained-release formulation of buprenorphine for analgesia in rats. J Am Assoc Lab Anim Sci 2011;50(2):198–204.
50. Peckham EM, Traynor JR. Comparison of the antinociceptive response to morphine and morphine-like compounds in male and female sprague-dawley rats. J Pharmacol Exp Ther 2006;316(3):1195–201.
51. Foley PL, Henderson AL, Bissonette EA, et al. Evaluation of fentanyl transdermal patches in rabbits: blood concentrations and physiologic response. Comp Med 2001;51(3):239–44.
52. Turner PV, Brabb T, Pekow C, et al. Administration of substances to laboratory animals: routes of administration and factors to consider. J Am Assoc Lab Anim Sci 2011;50(5):600–13.

53. Thomas A, Miller A, Roughan J, et al. Efficacy of intrathecal morphine in a model of surgical pain in rats. PLoS One 2016;11(10):e0163909–21. Bader M, ed.
54. Wenger S. Anesthesia and analgesia in rabbits and rodents. Journal of exotic pet medicine 2012;21(1):7–16.
55. Raffa RB, Friderichs E, Reimann W, et al. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an "atypical" opioid analgesic. J Pharmacol Exp Ther 1992;260(1):275–85.
56. Oyama T, Homan T, Kyotani J, et al. Effect of tramadol on pain-related behaviors and bladder overactivity in rodent cystitis models. Eur J Pharmacol 2012; 676(1–3):75–80.
57. Zegre Cannon C, Kissling GE, Goulding DR, et al. Analgesic effects of tramadol, carprofen or multimodal analgesia in rats undergoing ventral laparotomy. Lab Anim (NY) 2011;40(3):85–93.
58. Wolfe AM, Kennedy LH, Na JJ, et al. Efficacy of tramadol as a sole analgesic for postoperative pain in male and female mice. J Am Assoc Lab Anim Sci 2015; 54(4):411–9.
59. Taylor BF, Ramirez HE, Battles AH, et al. Analgesic activity of tramadol and buprenorphine after voluntary ingestion by rats (Rattus norvegicus). J Am Assoc Lab Anim Sci 2016;55(1):74–82.
60. Valle M, Garrido MJ, Pavón JM, et al. Pharmacokinetic-pharmacodynamic modeling of the antinociceptive effects of main active metabolites of tramadol, (+)-O-desmethyltramadol and (-)-O-desmethyltramadol, in rats. J Pharmacol Exp Ther 2000;293(2):646–53.
61. Souza MJ, Cox SK. Pharmacokinetics of orally administered tramadol in domestic rabbits (Oryctolagus cuniculus). Am J Vet Res 2008;69(8):979–82.
62. Egger CM, Souza MJ, Greenacre CB, et al. Effect of intravenous administration of tramadol hydrochloride on the minimum alveolar concentration of isoflurane in rabbits. Am J Vet Res 2009;70(8):945–9.
63. Grant GJ, Piskoun B, Lin A, et al. An in vivo method for the quantitative evaluation of local anesthetics. J Pharmacol Toxicol Methods 2000;43(1):69–72.
64. Cuvillon P, Nouvellon E, Ripart J, et al. A comparison of the pharmacodynamics and pharmacokinetics of bupivacaine, ropivacaine (with epinephrine) and their equal volume mixtures with lidocaine used for femoral and sciatic nerve blocks: a double-blind randomized study. Anesth Analg 2009;108(2): 641–9.
65. Flecknell PA, Liles JH, Williamson HA. The use of lignocaine-prilocaine local anaesthetic cream for pain-free venepuncture in laboratory animals. Lab Anim 1990;24(2):142–6.
66. Hedenqvist P, Orr HE, Roughan JV, et al. Anaesthesia with ketamine/medetomidine in the rabbit: influence of route of administration and the effect of combination with butorphanol. Vet Anaesth Analg 2002;29(1):14–9.
67. Murphy KL, Baxter MG, Flecknell PA. Anaesthesia with a combination of ketamine and medetomidine in the rabbit: effect of premedication with buprenorphine. Vet Anaesth Analg 2010;37(3):222–9.
68. Mickley GA, Hoxha Z, Biada JM, et al. Acetaminophen self-administered in the drinking water increases the pain threshold of rats (Rattus norvegicus). J Am Assoc Lab Anim Sci 2006;45(5):48–54. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=16995647&retmode=ref&cmd=prlinks.
69. Speth RC, Smith MS, Brogan RS. Regarding the inadvisability of administering postoperative analgesics in the drinking water of rats (Rattus norvegicus). Contemp Top Lab Anim Sci 2001;40(6):15–7.

70. Harcourt-Brown F. Textbook of rabbit medicine. Oxford (UK): Butterworth-Heinemann Medical; 2002.
71. Tiraloche G, Girard C, Chouinard L, et al. Effect of oral glucosamine on cartilage degradation in a rabbit model of osteoarthritis. Arthritis Rheum 2005;52(4): 1118–28.