

hronic pain in cats is commonly associated with malignancy, chronic inflammation, orthopedic disorders, chronic soft tissue injury, and nervous tissue injury. It is often difficult to recognize because the signs may be subtle, such as:²

- Hiding/withdrawing from humans or other animals in the home
- Reluctance to move or engage in normal activities
- Lack of appetite
- Elimination outside the litter box
- Aggressiveness.

Management presents several challenges for the veterinarian, including:

- Lack of approved products
- Potential for adverse drug reactions
- Difficulties in long-term drug administration
- Difficulty determining drug efficacy in "stoic" cats.

The most effective pain control often requires multimodal drug therapy: Opioids and nonsteroidal anti-inflammatory drugs (NSAIDs) are the 2 most commonly used drug classes; they may be supplemented with nutraceuticals and adjuvant analgesics.

OPIOIDS

Buprenorphine

Buprenorphine is a partial mu-agonist used to manage chronic pain in cats and is classified by the Drug Enforcement Administration (DEA) as a Schedule III controlled substance. Buprenorphine is not approved by the Food & Drug Administration (FDA) for use in cats.³

Administration. The common dose range is 0.01 to 0.03 mg/kg Q 6 to 8 H, which equates to 0.033 to 0.1 mL/kg of the injectable form (buprenorphine, 0.3 mg/mL).³ The drug may be administered SC, IM, IV, or buccally; buccal administration is the preferred route for chronic pain management.³

Buccal (transmucosal) administration of the injectable form is well tolerated (does not cause salivation), has a wide margin of safety, and produces predictable analgesia, especially for mild to moderate pain. It also makes the medication easier for owners to administer, since the volume required is small and can easily be squirted into the side of the cat's mouth.⁴

Cautions. Vomiting is rarely reported in cats; inappetance may occur after several days of therapy. Other side effects typical of opiates include behavioral changes (euphoria) and mydriasis. Generally, side effects can be diminished by a small reduction in dose.^{3,4}

FELINE CHRONIC PAIN MANAGEMENT: RECOMMENDED DRUG DOSES		
Drug	Formulation/Class	Dose
OPIOIDS		
Buprenorphine	Injectable solution (0.3 mg/mL)	 Transmucosal: Using the injectable formulation (0.3 mg/mL), administer 0.01–0.03 mg/kg, which equates to 0.033–0.1 mL/kg, Q 6–8 H
Tramadol	Tablets, oral com- pounded liquid	 Starting dose: 2 mg/kg PO Q 12 H commonly used Dose range: 1–4 mg/kg PO Q 8–12 H
NSAIDS		
Meloxicam*	Oral suspension (0.5 mg/mL)	 ISFM/AAFP Guidelines: Initial dose, 0.1 mg/kg PO; then 0.05 mg/kg PO Q 24 H Alternative long-term dosing: 0.05 mg/kg EOD or 0.025 mg/kg Q 24 H
Robenacoxib [†]	Tablets	• 1 mg/kg PO Q 24 H for up to 3 days§
ADJUNCT MEDICATIONS		
Amantadine	Antiviral drug	• 3–5 mg/kg PO Q 24 H
Amitriptyline	Tricyclic antidepressant	• 0.5–2 mg/kg PO Q 24 H
Gabapentin	Anticonvulsant	• 5–10 mg/kg PO Q 8–12 H
Prednisolone	Glucocorticoid	• 0.5–1 mg/kg PO Q 24 H

*Use of meloxicam oral suspension in cats is extra-label; †Approved for short-term use in cats \geq 5.5 lb (2.5 kg) and \geq 6 months of age; §ISFM/AAFP Guidelines recommend administration up to 6 days

Although overdoses may produce sedation and/or vomiting, life-threatening acute overdose is rare. If respiratory depression occurs, higher than normal doses of naloxone may be required for reversal (based on human studies), due to buprenorphine's high affinity for mureceptors.^{5,6}

Tramadol

Tramadol hydrochloride, a synthetic opioid, is approved for use in humans and is being used more frequently in veterinary medicine. Although not currently classified as a controlled substance by the DEA, tramadol is classified as a Schedule IV substance in some states and is reportable under state prescription drug monitoring programs. It is not approved for use in companion animals.

Mechanism of Action. This centrally acting medication is believed to (1) bind mu-opioid receptors and (2) weakly inhibit serotonin and norepinephrine reuptake. Both the parent compound and its primary metabolite, O-desmethyl-tramadol (M1) are active, and M1 is 200× more effective at mu-opioid binding.⁷ Cats have a lower M1 formation rate than dogs, but the lower metabolic clearance of tramadol in cats results in higher M1 concentrations.⁸

Administration. For treating feline chronic pain:

- Dose recommendations range from 1 to 4 mg/kg
 PO Q 8 to 12 H.
- 2 mg/kg PO Q 12 H is commonly used as a starting dose.³
- Based on cat's response to initial dose, dose/frequency will need to be evaluated.

Due to tramadol's serotonin-norepinephrine reuptake inhibitor mechanism, it may take up to 14 days to reach maximum analgesic effect. Compounding tramadol in a flavored oral suspension (1) improves tramadol's palatability, thereby increasing compliance and (2) provides more accurate dosing.

Cautions. Cats should be monitored for efficacy and adverse effects during tramadol therapy.

- Euphoria, dysphoria, and mydriasis, typical signs associated with opioid use in cats, have been reported following tramadol administration in cats.
- Signs of overdose include mydriasis, hypersalivation, tachycardia, agitation, lethargy and ataxia.³

Tramadol: Further Studies Needed

Although pharmacokinetics of tramadol have been studied in cats, 10 clinical studies determining efficacy and appropriate long-term dosing are lacking.

- One acute pain study in cats evaluated tramadol (2 mg/kg SC 1 H prior to surgery; then Q 8 H for 72 H post surgery) alone and in combination with vedaprofen for the treatment of ovariohysterectomy pain.
- Tramadol alone reduced pain when compared to placebo, but tramadol and vedaprofen combined produced better analgesia than either drug alone.⁸

NSAIDS

NSAIDs are used for their antipyretic, analgesic, and anti-inflammatory properties. Most of the published data on their use in cats relate to short-term (often perioperative) therapy, but growing evidence suggests they may be useful for chronic pain management with appropriate, individualized dosing and continuous patient monitoring.²

Considerations

Two important factors should be considered when using NSAIDs in cats:

- 1. Cats receiving NSAIDs may have increased risk for adverse drug reactions and toxicity compared to dogs and humans receiving the same class of drug.
- 2. Rate of metabolism varies inconsistently (1) among individual cats and (2) in cats when compared to other species.¹¹⁻¹³

When administering NSAIDs to cats for long-term chronic pain management, it is essential to:

- Carefully monitor patient's overall health status, concurrent disease states, signs of adverse events, and improvement in quality of life.
- Evaluate liver and renal function periodically; frequency is determined by risk factors, such as age, health status, and concurrent medications.
- Titrate NSAIDs to the lowest effective dose for long-term use.
- Advise owner to discontinue medication immediately if the cat stops eating or drinking. Recommend use of a moist food to help with hydration status.²

Meloxicam

Meloxicam (Metacam, us.boehringer-ingelheim.com) is FDA-approved for use in cats for postoperative pain. Although the oral liquid suspension is not approved for cats, it has been used extra-label for both acute and chronic pain management.

Administration.

- The FDA-approved dose in cats is a single dose,
 0.3 mg/kg SC, of the injectable solution.
- The ISFM/AAFP recommended dose is 0.1 mg/kg PO for day 1; then 0.05 mg/kg PO daily.²
- Others recommend a maintenance dose of 0.05 mg/kg every other day or 0.025 mg/kg daily.¹⁴

For further information, see **Meloxicam: Safe to Use Long-Term?**

Cautions. Concurrent use of other NSAIDs, glucocorticoids, hepatotoxic, and nephrotoxic drugs should be avoided during meloxicam therapy. Other drugs that must be used cautiously, if at all, are angiotensin-converting enzyme inhibitors, anticoagulants, digoxin, fluconazole, and phenobarbital.

Robenacoxib

Robenacoxib (Onsior, ah.novartis.com) is FDA-approved for control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy, and castration in cats. This NSAID, which has high selectivity for inhibition of COX-2 (see **Review of Cox Activity**), may hold promise for management of chronic pain in cats.

Administration. Robenacoxib is approved for short-term (up to 3 days) administration in cats ≥ 5.5 lb (2.5

kg) and \geq 6 months of age at a dose of 1 mg/kg PO Q 24 H. In Europe, it is approved for administration up to 6 days.

Cautions. Although 2 safety studies of young, healthy cats receiving higher-than-recommended doses over a period of 42 days revealed no toxicologically significant effects, ¹⁶ there are no published guidelines for long-term use in feline chronic pain management.



Meloxicam: Safe to Use Long-Term?

In 2010, the FDA issued the following boxed warning:

Repeated use of meloxicam in cats has been associated with acute renal failure and death. Do not administer additional injectable or oral meloxicam to cats.

Consensus Guidelines

However, that same year, the International Society of Feline Medicine (ISFM) and American Academy of Feline Practitioners (AAFP) released consensus guidelines recommending long-term daily dosing of meloxicam oral suspension for inflammation and pain in chronic musculoskeletal conditions.

Study Results of Long-Term Use

A recent retrospective case study provides support for meloxicam use for feline chronic pain management, even in older cats with chronic renal failure.¹⁵

- Twenty-two cats with chronic renal failure (median age, 15.5 years) received meloxicam for a median treatment duration of 467 days, with titration to the lowest effective dose.
- The results suggested that a long-term daily dose of 0.02 mg/kg can be safely administered to some clinically stable cats over 7 years of age even in the presence of chronic kidney disease.
- However, further studies are warranted due to the small number of cats studied.

Read the ISFM and AAFP Consensus Guidelines: Long-Term Use of NSAIDs in Cats at isfm.net/toolbox/info_sheets/NSAIDs_guidelines.pdf.



Review of COX Activity

The effects of NSAIDs are achieved by inhibiting production of prostaglandins and leukotrienes from arachidonic acid by the enzymes cyclooxygenase (COX) and 5-lipoxygenase, respectively. The 2 primary isoforms of COX are:

- COX-1 enzymes, described as predominantly constitutive, help produce prostaglandins that protect gastric mucosa and maintain normal platelet function and renal perfusion.
- COX-2 enzymes are primarily inducible, showing dramatic upregulation during the inflammatory process, in which they play a central role.

NSAIDs can be categorized as:

- Nonselective COX inhibition: Thought to cause classic NSAID side effects, including gastrointestinal (GI) ulceration, anorexia, vomiting, diarrhea, hepatotoxicity, and renal toxicity.
- COX-2 preferential: Greater suppression of COX-2 than COX-1 (ie, metacam)²
- COX-2 selective: Virtually no COX-1 suppression at therapeutic doses (ie, robenacoxib)²

ADJUNCT MEDICATIONS

Although chronic pain may be adequately controlled in some cats using a single agent, such as an opioid or NSAID, other cats may need a combination of both; in some cats with severe pain adjunct medications can be beneficial. Selection of appropriate adjuncts depends on type of pain and concurrent medications.

Amantadine

Amantadine, an **antiviral drug** with *N*-methyl-D-aspartate receptor antagonist properties, is primarily used as part of multimodal analgesia for cancer or neuropathic pain. It is generally administered in conjunction with NSAIDs to provide improved pain control; it can also be combined with an NSAID and opioid or other adjuncts.

Administration. Amantadine, available as a 100-mg capsule, must be compounded to facilitate accurate dosing. The recommended dose in cats is 3 to 5 mg/kg PO Q 24 H.^{3.17} Amantadine is also available as an oral liquid, but it is usually not palatable to cats.³

Cautions.

- *Side Effects*: Although no adverse drug event profile exists for cats, reported side effects in dogs include agitation, loose stools, and flatulence, especially early in therapy.
- Toxicity: This drug appears to have a low safety margin; therefore, accurate dosing is crucial. A toxic dose of 30 mg/kg has been reported in cats, although behavioral effects have been noted at 15 mg/kg. Signs of overdosage documented in

- humans include cardiac arrhythmias, hypertension, pulmonary edema, central nervous system toxicity (eg, tremors, seizures, agitation, coma) hyperthermia, renal dysfunction, and respiratory distress³
- *Concurrent Disease:* Based on human information, use this drug cautiously in cats with liver disease, kidney disease (dose reduction may be required since drug is renally eliminated), congestive heart failure, or seizure disorders.
- Interactions:
 - » Trimethoprim/sulfa combination drugs may decrease excretion of amantadine, yielding higher blood levels.
 - » Anticholinergic drugs, and other drugs with anticholinergic effects, such as antihistamines, may increase the anticholinergic effects of amantadine, resulting in xerostomia, urine retention, increased intraocular pressure, constipation, and excitement in cats.
 - » Central nervous system (CNS) stimulants administered concurrently may increase CNS stimulatory effects, resulting in increased agitation.

Amitriptyline

Amitriptyline, a **tricyclic antidepressant**, is usually administered in combination with an NSAID for feline chronic pain of neuropathic origin; it may also be synergistic with opioids.¹⁸

Administration. The recommended dose is 0.5 to 2 mg/kg PO O 24 H.^{3,14}

Cautions.

- *Side Effects:* Amitriptyline is usually well tolerated in cats, although some drowsiness/sedation may occur. Other side effects reported in cats include hypersalivation (due to bitterness of tablets), urinary retention, anorexia, thrombocytopenia, neutropenia, unkempt hair coat, vomiting, ataxia, disorientation, and cardiac conductivity disturbances.³
- Concurrent Disease: Use amitriptyline with extreme caution in patients with seizure disorders, since tricyclic agents can decrease seizure thresholds. Also use with caution in patients with thyroid disorders, cardiac arrhythmias, keratoconjunctivitis sicca, glaucoma, hepatic disorders (drug metabolized in liver to active/inactive metabolites), diabetes, or adrenal tumors.
- *Interactions:* Cats receiving both amitriptyline and tramadol should be closely monitoired for serotonin sydrome (SS) due to these drugs' serotonergic activity. Reported signs of SS in dogs and humans include hyperactivity; increased heart rate, blood pressure, and/or body temperature; tremors/shivering; dilated pupils; dyspnea; ataxia; vomiting; and diarrhea. ¹⁹ If SS is suspected, immediately discontinue both drugs and initiate treatment. Avoid this drug combination in patients with seizure disorders or those at risk for seizures.

Gabapentin

Gabapentin, an anticonvulsant drug, is used in cats as an adjunct for chronic pain management, especially neuropathic pain; it has been used in combination with opioids, NSAIDs, and amantadine. This drug can prevent *allodynia* (sensation of pain from nonnoxious stimulus) and byperalgesia (increased sensitivity to pain response).

Administration. A dose of 5 to 10 mg/kg PO Q 8 to 12 H is commonly recommended.

Cautions.

- Side Effects: Sedation and/or ataxia are the most common adverse effects. They can be alleviated by initiating therapy at a low dose; then gradually titrating up to effect.
- Concurrent Disease: Use with caution in patients with renal dysfunction (dose reduction may be required since drug is renally eliminated).
- Interactions:
 - » Antacids and gabapentin should be administered 2 hours apart to prevent reduced bioavailability of gabapentin.3
 - » Hydrocodone may increase efficacy and/or adverse effects of gabapentin, while gabapentin decreases the efficacy of hydrocodone, based on human literature.20

Prednisolone

Prednisolone, a glucocorticoid, can be particularly effective for cancer pain, especially pain associated with significant inflammation, such as feline squamous cell carcinoma of the oral cavity.

Administration. The recommended dose in cats is 0.5 to 1 mg/kg PO Q 24 H.¹⁷ Always use prednisolone—while other species can convert prednisone to prednisolone in the liver, cats do not absorb or convert prednisone efficiently.21

Cautions. Do not use concurrently with NSAIDs.

NUTRACEUTICALS

Nutraceutical use has become a common adjunct in chronic pain management for cats with arthritic conditions, especially since these supplements, such as glucosamine and chondroitin sulfate, are readily available as over-the-counter products.

Administration. A dose of 15 mg/kg (based on the chondroitin component) PO Q 12 to 24 H is recommended for glucosamine and chondroitin combination products.17

Cautions. These products appear safe for feline use as part of a multimodal pain management protocol.22 Veterinarians and consumers must, however, rely on the reputation of the manufacturer when selecting products for their pets (see Nutraceuticals: Study Results).

Nutraceuticals: Study Results

Since there are many of these products on the market and they are not FDA approved, skepticism has arisen in the scientific community regarding product quality.

Anecdotal evidence suggests that nutraceuticals improve clinical signs associated with degenerative joint disease; however, little evidence-based research is available.

- Preliminary studies using a combination of glucosamine/chondroitin sulfate and avocado/ soybean unsaponifiables demonstrated reduction of inflammation associated with feline osteoarthritis.23,24
- Over-the-counter products (n = 32) were evaluated to determine whether they contained the labeled amount of active ingredients; significant differences existed between stated and measured amounts in a number of products.25

IN SUMMARY

Although chronic pain management in cats presents many challenges for veterinarians and pet owners, a multimodal drug protocol can produce effective results. Safety is maintained by:

- Keeping the patient's overall health status stable
- Individualizing and adjusting drug doses as needed
- · Monitoring for signs of improvement, adverse reactions, toxicity, and interactions.

AAFP = American Association of Feline Practitioners; CNS = central nervous system; COX = cyclooxygenase; FDA = Food & Drug Administration; GI = gastrointestinal; ISFM = International Society of Feline Medicine; NSAID = nonsteroidal anti-inflammatory drug

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