Outpatient Oral Analgesics in Dogs and Cats Beyond Nonsteroidal Antiinflammatory Drugs: An Evidence-based Approach

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INTRODUCTION

Treatment of outpatient pain in dogs and cats can be rewarding for the owners and veterinarians. Nonsteroidal antiinflammatory drugs (NSAIDs) are commonly administered to dogs and occasionally cats for controlling pain in an outpatient setting. There

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are several NSAIDs approved by the US Food and Drug Administration (FDA) for dogs, with label indications of postoperative pain relief and management of osteoarthritis and there are a few that are FDA approved for cats for postoperative pain. Meloxicam is also approved by the European Medicines Agency for long-term control of musculoskeletal disorders in cats. Most animals tolerate NSAIDs well, with an expected 5% to 10% of patients having to discontinue treatment because of adverse effects, and up to 10% to 12% of patients potentially not responding to therapy. Adverse effects such as vomiting, diarrhea, gastrointestinal (GI) erosion/ulceration, nephropathy, or hepatopathy can occur. In addition, contraindications/precautions such as underlying renal disease, underlying hepatic disease, corticosteroid administration, or Cushing disease may preclude the use of NSAIDs. Therefore it is important to have knowledge of potential alternate therapeutics available and an understanding of the amount of information available supporting their use in dogs in cats (Table 1).

PHARMACOKINETICS AND THEIR APPLICATION TO ANALGESIC DOSAGE DESIGN

Pharmacokinetic studies are performed to describe the disposition of a drug in a particular species, after specific routes of administration, and at specific doses. Changes in route of administration, species, and dose can result in changes in the pharmacokinetic parameters. Therefore extrapolation of pharmacokinetic parameters to other species, routes of administration, or doses may not be accurate. In addition, many studies assess the pharmacokinetics of a drug after a single dose, but the pharmacokinetics may change with repeated doses, so extrapolating to multiple doses may not be accurate.1,2

Some drugs are metabolized to produce active metabolites that can contribute to the beneficial (and adverse) effects of the drug.3 Some studies include the measurement and pharmacokinetics of active metabolites, but not all studies measure active metabolites and as such are incomplete descriptions of the potential factors contributing to the effects of the drugs.

Pharmacokinetic studies are useful in describing the extent and duration of drug exposure after an administered dose. Data derived from pharmacokinetic studies may be used to generate dose and interval recommendations to achieve and maintain desired concentrations, but that may not confer efficacy because there may be species-specific differences in the concentration or dose response to the drug. However, these recommendations are useful for designing experimental model studies, case studies, or controlled clinical trials.

Pharmacokinetic data are often used as a method of determining drug dosages. However, without corresponding data associating plasma concentrations with a clinical effect, the predictions may not be accurate because of differences in response to the drug. Pharmacokinetic studies provide a basis for potential effects or for dosages used in experimental study designs and controlled clinical trials.

Because many drugs are administered orally to dogs and cats, oral bioavailability is an important pharmacokinetic parameter. Oral bioavailability is the rate and extent of drug absorption after oral administration. However, bioavailability is often used to express only the fraction of dose absorbed, and it is used in that context in this article. High oral bioavailability implies that a large fraction of the dose is absorbed intact into systemic circulation after oral administration. Low oral bioavailability implies that a small fraction of the drug is absorbed.

Some factors affecting bioavailability include absorption of the drug from the site of administration (eg, a drug that is not absorbed has a low bioavailability), active efflux of the drug back into the lumen of the intestines after absorption, and presystemic
<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA Approved for Dogs or Cats?</th>
<th>Strength of Evidence</th>
<th>Relative Cost</th>
<th>Dose Frequency</th>
<th>DEA Scheduled</th>
<th>Other Notes</th>
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<tr>
<td>Polysulfated glycosaminoglycans</td>
<td>Yes, dogs</td>
<td>High</td>
<td>Moderate</td>
<td>Twice weekly</td>
<td>No</td>
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<td>Amantadine</td>
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<td>Moderate</td>
<td>Moderate</td>
<td>q 12–24 h</td>
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<td>—</td>
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<td>Tramadol</td>
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<td>Low</td>
<td>Low</td>
<td>q 6–8 h</td>
<td>No</td>
<td>Acetaminophen combinations toxic to cats</td>
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<td>Gabapentin</td>
<td>No</td>
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<td>High</td>
<td>q 8 h</td>
<td>No</td>
<td>—</td>
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<tr>
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<td>Low</td>
<td>High</td>
<td>q 12 h?</td>
<td>CV</td>
<td>—</td>
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<tr>
<td>Codeine</td>
<td>No</td>
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<td>CII–CIII</td>
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<td>—</td>
<td>CII</td>
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*Abbreviations: DEA, Drug Enforcement Agency; q, every.*

*Some US states have restrictions on tramadol prescribing.*
metabolism (metabolism of the drug after absorption, but before the drug entering systemic circulation). Codeine is a drug that is completely absorbed after oral administration to dogs, but only 4% of the parent drug reaches systemic circulation as codeine; the remaining 96% enters the systemic circulation as the active metabolite, codeine-6-glucuronide. Therefore, despite complete codeine absorption in the dog, the oral bioavailability is only 4%.

Neither a high or low bioavailability absolutely predicts whether a drug can be effectively administered by a particular route. For example, diazepam has a low rectal bioavailability, but can be effective in controlling seizures in dogs because many active metabolites are formed during first-pass metabolism, producing a therapeutic effect. In contrast, acetaminophen is well absorbed in dogs, with about a 50% oral bioavailability, but, because its elimination half-life is less than 1 hour, it requires a 4-hour (or shorter) dosing interval to maintain desired concentrations, which is not possible for many owners.

Although low oral bioavailability can occasionally be overcome by increasing the drug dose, many times this is not an advisable strategy. Drugs with a low bioavailability also tend to have variable bioavailability, which makes dosing adjustments difficult. It is common for a drug with low oral bioavailability to have a 5-fold to 10-fold range in bioavailability, and the amount for any given animal on any given day can be within that range. Therefore selecting a dose with the intent to reach a desired plasma concentration can be difficult. For example, the oral bioavailability of meperidine ranged from 2% to 25% in 3 beagle dogs. In addition, drugs may have dose-dependent changes in bioavailability caused by saturated absorption or metabolism pathways. Disproportional amounts of drug may be absorbed with changes in dose, which could produce drug toxicity. In contrast, less than proportional increases in the amount of drug absorbed can occur with increasing doses; for example, doubling the dose may only increase the total amount of drug absorbed from 4% to 5%.

CONTROLLED CLINICAL TRIALS

Controlled clinical trials are the best method of evaluating a drug for clinical use. The best study design for controlled clinical trials includes both positive and negative controls, has evaluators and administrators blinded to treatment to avoid bias, and randomly assigns animals to treatment groups to avoid bias. An excellent review of the design of clinical trials is available.

Positive controls are needed to show that the study design can effectively determine the beneficial effects of the test treatment. For example, a study that includes only a negative control may generate a result of no significant difference between the test drug and the negative control. Without a positive control, it is not possible to determine whether the result is caused by a lack of effect of the test drug or by the evaluating method being unable to differentiate lack of benefit from a positive benefit. A negative control is needed to show that any measured benefit is the result of drug administration and not from observer bias or inability of the evaluation method to identify lack of an effect. Although a placebo effect is not typically thought of as occurring in animals, it has been documented and can be substantial: up to 25% (1 in 4 animals) as assessed by veterinarians and up to 39% (2 in 5 animals) as assessed by owners were reportedly improved on the Freedom of Information (FOI) summary for carprofen (New Animal Drug Application [NADA] 141-053). The percentage of responders in the placebo group, as evaluated by veterinarians, was 33% (1 in 3 animals) for the FOI for polysulfated glycosaminoglycans (NADA 141-038).

Some potential limitations of controlled clinical trials include that efficacy determined for one indication may not extrapolate to other disease conditions, the dose
administered may not have been correct, the evaluating methods may not have been appropriate for the study, the study may not have had enough statistical power (sample size too small) to detect a true difference, the data may not be reproducible, and a perceived improvement was caused by random variability despite achieving a significant difference. Examples include that a drug effective for relieving osteoarthritis pain may not be effective for postoperative orthopedic pain and that the dose administered may have been too low and therefore lack of effect was only caused by lack of sufficient concentrations in the body.

Another major limitation of controlled clinical trials evaluating analgesics is that any method of evaluating efficacy is confounded by other factors. For example, pressure mat analysis, force plate, and lameness scores can be affected by gait independently of pain; owner questionnaires can have biased answers; and physiologic measurements can be affected by factors other than pain, such as stress of transport and evaluation. There is not currently a universally accepted measure of analgesia that is not confounded by other factors.

**Experimental Models Assessing Analgesics in Animals**

Experimental studies can be used to assess analgesic drugs. The most common types of models use thermal transducers (heat), mechanical stimulation (von Frey devices), electrical stimulation, or chemical stimulation (urate crystals) to produce a noxious stimulus. However, not all of the methods are selective for pain/analgesia. For example, thermal transducers produce heat, and an animal’s response may be caused by temperature changes and not pain; mechanical stimulation may produce a response because of pressure of the device before activation of pain pathways; electrical stimulation can produce a response because of muscle twitching independently of pain; and chemical stimulation produces inflammation in addition to pain. Another limitation of experimental studies is that they may not extrapolate to naturally occurring pain and analgesia. A complete review of pain models is available. Despite their limitations, experimental models can be helpful for providing a rational basis for use of analgesic drugs in veterinary patients. There is currently no gold standard and every model has limitations.

**Clinical Impressions of Analgesic Efficacy**

Clinical impressions are one of the most common sources of information on drug use in veterinary medicine, especially with the advent of the Internet and discussion forums. However, clinical impressions are the least reliable sources of information on drug efficacy. Clinical impressions do not account for the placebo effect, which occurs in up to 2 in 5 animals when owners or veterinarians evaluate the animal (NADA 141-053). Clinical impressions also do not control for bias from the veterinarian or owner, both of whom think that, if they are doing something, it has to be helping the animal. Clinical impressions also do not control for naturally occurring fluctuations in the severity of pain. In addition, veterinarians may lose follow-up on a case for a variety of reasons and as such may recall treating a patient, but not know the outcome and assume a positive outcome when it may or may not have occurred.

**Specific Pharmaceutical Therapies**

*Polysulfated Glycosaminoglycans*

Polysulfated glycosaminoglycans (PSGAGs) are an FDA-approved injectable product for the control of signs associated with noninfectious degenerative and/or traumatic
arthritus of canine synovial joints. The mechanism of action of PSGAG is not known. The drug may act by decreasing catabolic enzymes within the affected joints and enhances anabolic enzymes based on in vitro studies (NADA 141-038). A placebo-controlled clinical trial in which PSGAG was administered at 4.4 mg/kg (2 mg/lb) body weight intramuscularly (IM) to dogs with traumatic or degenerative joint disease supported the approval. The PSGAG significantly improved range of motion and total orthopedic score compared with placebo at 5 weeks. The percentage of responders in the PSGAG group was significantly higher than in the placebo group (65% vs 33%) at 5 weeks.

Because PSGAG is an FDA-approved drug for dogs, it is expected to provide beneficial effects for the management of noninfectious osteoarthritis when administered at 4.4 mg/kg body weight IM twice weekly for 4 weeks. There are currently no data supporting the use of PSGAG in cats, but there are no data refuting its use in cats. There are no published safety data available in cats. The current cost of PSGAG is moderate. The results and efficacy of the approved injectable product should not, and do not, support the use of other products such as oral glucosamine formulations.

**Amantadine**

Amantadine is an antiviral drug, but possesses other effects, including increasing central nervous system dopamine concentrations, and it is also an N-methyl-D-aspartate (NMDA) antagonist. As an NMDA antagonist, amantadine may antagonize central pain sensitization and decrease tolerance to analgesics such as opioids. Amantadine decreased opioid consumption in postoperative human patients, reduced pain in postherpetic neuralgia in humans, and has had mixed results with neuropathic pain in humans. Amantadine is not expected to provide analgesic effects as a sole therapy, but may enhance the analgesic effects of NSAIDs, opioids, or gabapentin/pregabalin. No FDA-approved veterinary formulations are available.

The pharmacokinetics of amantadine have been incompletely described in dogs. Based on urinary excretion studies in 2 dogs, amantadine seems to be well absorbed in dogs, about 10% is metabolized to N-methylamantadine, and the half-life of amantadine was short: 5 hours after 30 mg/kg. No reports are available assessing the activity or lack thereof for the metabolite. Dogs administered amantadine 50 mg/kg every 24 hours by mouth for 30 days had negligible amounts of drug in tissue samples collected 24 hours after the last dose with the investigators concluding that a dose of amantadine is eliminated within 24 hours. In cats, the pharmacokinetics are better described, with high oral bioavailability and a short half-life: approximately 5.5 hours after 5 mg/kg by mouth. In contrast, the elimination half-life in humans is 15 hours. Because of the short half-life, dosing every 12 hours may need to be used in dogs and cats.

Safety studies have not specifically been reported for amantadine in dogs or cats. However, 50 mg/kg every 24 hours were administered to dogs for 30 days without lethality.

No preclinical studies of amantadine analgesic effects are available in dogs. Amantadine did not have a significant effect on oxymorphone antinociception to thermal stimulus in normal cats. The lack of effect is not surprising because amantadine is expected to produce effects when pain or central sensitization is already present and is not expected to decrease acute stimulus. Therefore the lack of effect in this experimental study should not be interpreted as a lack of potential clinical effects in naturally occurring pain.

A randomized, placebo-controlled and blinded clinical trial evaluated the efficacy of adding amantadine to meloxicam for the management of NSAID-refractory hind limb
osteoaarthritis pain in dogs. Significant improvement was noted using client-specific outcome measures for activity in the amantadine treatment group (3–5 mg/kg by mouth every 24 hours) on day 42 of treatment, but not on days 7 or 21. As mentioned previously, administration every 12 hours may be a better dosage because of the rapid elimination in dogs and may result in greater efficacy. The study evaluated amantadine in combination with only 1 NSAID so it is unclear whether the same effect would be observed with other NSAIDs. No controlled clinical trials are available for amantadine use in cats.

Based on the currently available data, amantadine (3–5 mg/kg every 24 hours) may provide benefit when added to meloxicam in dogs, but the dosing frequency of amantadine may need to be increased to every 12 hours. There are currently no data supporting the use of amantadine in cats, but there are no data refuting its use in cats. The current cost of amantadine is moderate.

Tramadol

Tramadol is FDA approved for the management of moderate to moderately severe pain in humans. Tramadol is metabolized into at least 30 different metabolites, but only tramadol, O-desmethyltramadol (ODM), and N,O-didesmethyltramadol (DDM) have been associated with pharmacologic effects. Tramadol administration produces analgesia, which is partially blocked by naloxone (mu opioid antagonist), yohimbine (alpha-2 antagonist), ketanserin (serotonin 5-hydroxytryptamine [HT]-2 antagonist), and ondansetron (5HT-3 antagonist), suggesting that all 3 receptor systems contribute to the analgesic effects. Other studies have also suggested that tramadol produces antagonist effects at muscarinic M1 receptors that can be overcome by acetylcholine administration. Further studies have shown that the mu opioid effects are primarily caused by ODM with some secondary effects of DDM, whereas the serotonin and norepinephrine effects are caused by tramadol and ODM, and the antimuscarinic effects are caused by ODM.

Pharmacokinetic studies in dogs have shown that dogs do not produce ODM as a substantial metabolite after tramadol administration; however, they do produce DDM. Therefore dogs are not expected to have substantial opioid effects after tramadol administration. Plasma concentrations of tramadol after administration of 10 mg/kg by mouth to dogs were slightly less than the plasma concentrations achieved in humans administered 100 mg single doses, but the concentration of ODM was 10 times less in dogs compared with humans. The elimination half-life of tramadol in dogs is more rapid (1.1 hours) compared with humans (5.6 hours). The production of DDM, which has an elimination half-life of 3.6 hours in dogs, may produce some opioid effects in dogs. Repeated doses of tramadol either decreased drug absorption or enhanced presystemic metabolism of tramadol in dogs, in which a 60% to 70% decrease in tramadol plasma concentrations resulted after just 8 days of treatment (20 mg/kg by mouth). The effects of multiple-day administration on the metabolites ODM and DDM were not reported.

In contrast with dogs, cats produce high concentrations of ODM after tramadol administration and as a result have prominent opioid effects. The concentrations of ODM after 5.2 mg/kg tramadol by mouth were 10 times higher than ODM concentrations in humans after 100 mg by mouth. The terminal half-life of ODM after oral tramadol in cats was 4.5 hours, suggesting that administration every 12 hours may be appropriate in cats. The plasma concentrations of tramadol and ODM were dose proportional from 0.5 to 4 mg/kg by mouth. The pharmacokinetics of repeated doses of tramadol have not been reported in cats.
A pressure pain threshold model was used to assess the effects of oral tramadol (10 mg/kg by mouth) in dogs. Significant increases in thresholds were observed only at 5 and 6 hours after administration. It is unclear how mechanical antinociceptive effects translate to clinical analgesic effects.

The effects of tramadol on thermal thresholds in cats have been reported. The thermal thresholds exceeded the 95% confidence interval at 0.75, 3, and 6 hours after 1 mg/kg tramadol, but not at 1, 2, 4, 8, and 24 hours. A dose titration study evaluated the effects of tramadol dosed 0.5 to 4 mg/kg by mouth in cats using a thermal threshold model. Thermal thresholds increased proportionally with increased doses. The duration of increased thresholds were also related to the dose, with 2 mg/kg producing significant effects from less than 6 hours to up to 13 hours after administration, 3 mg/kg producing significant effects from 9 to 12 hours after administration, and 4 mg/kg producing significant effects from 10 to 16 hours after administration.

There are few studies assessing the effects of tramadol administration to clinical canine patients in controlled clinical trials. Only 1 study reports the effects of oral tramadol in a blinded study using positive and negative controls, and these were in patients with osteoarthritis. The incorporation of both positive and negative controls is important because an effect (perceived improvement) occurred in the placebo group using an owner-completed canine brief pain inventory questionnaire. However, significant improvement was noted in the positive control group (carprofen, 2.2 mg/kg twice a day) and tramadol (4 mg/kg 3 times a day) group compared with the placebo (administered 3 times a day). Plasma concentrations of carprofen and tramadol were measured 3 hours after the first dose and last dose (14 day). The plasma concentrations of carprofen were within the expected plasma concentrations. The plasma concentrations of tramadol were low (39.3 ± 35.3 ng/mL) 3 hours after the first dose and were significantly decreased 3 hours after the last dose (7.1 ± 8.8 ng/mL), and not even detected in 4 of 11 dogs, again suggesting decreased bioavailability with multiple doses. In comparison, the plasma concentrations of tramadol in humans after 100 mg by mouth peak at 308 ng/mL 2 to 3 hours after dosing. The plasma concentrations of ODM and DDM were not reported.

There are few studies assessing the effects of tramadol administration to clinical feline patients in controlled clinical trials. Only 1 study reports the effects of tramadol using a blinded study with negative controls and these were in patients after ovariohysterectomy. Treatment groups included placebo, the NSAID vedaprofen (0.5 mg/kg by mouth), tramadol (2 mg/kg subcutaneously [SC]), and the combination of tramadol and vedaprofen. Patients were evaluated with a composite pain scale. All of the patients receiving placebo and vedaprofen received rescue analgesia, 50% of the tramadol patients received rescue analgesia, and none of the vedaprofen and tramadol group received rescue analgesia. The composite pain scale was significantly lower for the combination of vedaprofen and tramadol from 1 to 56 hours after surgery, but not significantly lower in any of the other treatment groups for more than 1 time point compared with placebo.

Tramadol is overall well tolerated in dogs. Administration of single oral doses of 450 mg/kg was not fatal in an unstated number of dogs. Administration of 40 mg/kg per day to 8 dogs was well tolerated for 1 year, with mydriasis and reduced body weight observed. Adverse effects of tramadol overdose include restlessness, difficulty walking, salivation, vomiting, tremors, and convulsions. Anecdotal reports suggest that diazepam is effective in controlling tramadol-induced convulsions. Similar adverse effects are expected in cats with acute tramadol overdoses.

Adverse effects such as nausea and anorexia, and occasionally sedation, can occur in dogs with routine dosages of tramadol. According to the label, tramadol may also
decrease the seizure threshold in humans and as such it would be best to avoid use in animals prone to seizures. Tramadol is bitter tasting and can result in profuse salivation and retching if the animal tastes the drug. Similar adverse effects are expected in cats with routine doses of tramadol.

A case series describing 3 postoperative dogs reported higher potential of GI adverse effects when tramadol was combined with deracoxib, an NSAID, than expected from an NSAID alone.23 There are not currently any contraindications listed for tramadol use with NSAIDs in humans. However, there is documentation of potential interactions with other drugs affecting serotonin reuptake, including selective serotonin reuptake inhibitors (eg, fluoxetine, paroxetine) and serotonin-norepinephrine reuptake inhibitors (SNRIs; eg, venlafaxine, duloxetine) increasing the risk of GI ulcers administered alone or in combination with NSAIDs.24 In addition, a case series in humans identified that patients prone to GI adverse effects of NSAIDs had a higher risk of GI perforation caused by tramadol administered alone.25 The mechanism of action is thought to be serotonin-enhanced gastric acid secretion through vagal stimulation. Another potential mechanism is decreased platelet aggregation caused by serotonin depletion within the platelets, because platelets do not synthesize serotonin and rely on transport to accumulate serotonin. On activation of platelets, serotonin is released, resulting in vasoconstriction and subsequent enhanced hemostasis. The risk of GI bleeding in humans administered drugs that inhibit serotonin reuptake and NSAIDs is decreased if acid-suppression therapy (eg, H2 antagonists such as famotidine or proton pump inhibitors such as omeprazole) is coadministered. Therefore it may be prudent to administer acid-suppression therapy to dogs and cats when tramadol is administered concurrently with an NSAID to decrease the risk of GI adverse effects.

The use of tramadol with other drugs that affect serotonin reuptake or metabolism should be avoided because of the risk of serotonin toxicity. Monoamine oxidase inhibitors (selegiline), tricyclic antidepressants (TCAs; eg, amitriptyline, clomipramine), selective serotonin reuptake inhibitors (fluoxetine, paroxetine), and SNRIs (venlafaxine) should not be administered concurrently with tramadol. Serotonin syndrome has been documented in dogs, with signs such as tremors, rigidity, myoclonus, seizure, hyperthermia, salivation, and even death.26

Because of the high concentrations of ODM in cats administered tramadol, opioid-mediated adverse effects can occur in this species. Sedation, mydriasis, dysphoria or euphoria, constipation, and vomiting can occur in cats.

There are some data supporting tramadol use in clinical veterinary patients, but more studies need to be conducted to confirm its efficacy and safety in dogs and cats. Dogs may benefit from tramadol administered 4 to 10 mg/kg by mouth 3 times a day. However, the long-term efficacy of tramadol may decrease with time. Cats may benefit from tramadol after surgery when combined with an NSAID. Other studies are needed to fully describe the potential uses of tramadol in dogs and cats.

Tramadol is not currently a Drug Enforcement Agency (DEA) scheduled drug. However, numerous US states have enacted laws requiring special handling as a potential drug of abuse, including classifying it as a schedule IV (CIV) drug. Therefore any prescribers should check with their respective boards of pharmacy to determine current requirements for tramadol prescriptions. Tramadol has a moderate potential for diversion or misuse. The current cost of tramadol is low.

**Gabapentin**

Gabapentin is FDA approved as an anticonvulsant and as an analgesic for postherpetic neuralgia for human use. Gabapentin enacarbil (an extended-release
Gabapentin (gabapentin ester) is also FDA approved for the treatment of restless legs syndrome in humans. Gabapentin is a structural analog of gamma-aminobutyric acid (GABA), but does not bind directly to the GABA receptors. The mechanisms for gabapentin’s anticonvulsant and analgesic effects have not been definitively identified. However, gabapentin does bind to the alpha-2/delta subunit of the voltage-gated calcium channel decreasing the release of excitatory neurotransmitters. Gabapentin also increases the brain concentrations of GABA either through increased GABA synthesis, increased vesicular release, or decreased GABA metabolism. A thorough review of potential mechanisms of action of gabapentin has been published.\textsuperscript{27}

The pharmacokinetics of gabapentin have been described in dogs\textsuperscript{28} and cats.\textsuperscript{29} Gabapentin exhibits less than proportional increases in plasma concentrations with increasing doses following oral administration because of saturation of active transporters in the GI tract. Gabapentin is primarily eliminated as unchanged drug in most species except dogs, in which metabolism to N-methyl-gabapentin accounts for approximately 40\% of drug disposition.\textsuperscript{30} The terminal half-life of gabapentin is short in dogs (3–4 hours) and cats (~3 hours), necessitating dosing at least every 8 hours to maintain minimum targeted concentrations associated with efficacy in humans (2 \( \mu \text{g/mL} \)). Therefore dosing compliance is a limitation of gabapentin therapy in dogs and cats. A dosage of 10 to 20 mg/kg every 8 hours maintains targeted concentrations in dogs and cats. The pharmacokinetics of gabapentin enacarbil have not been published in dogs or cats, therefore it is unknown whether an extended dosing interval is possible with gabapentin enacarbil in dogs or cats.

Gabapentin failed to show an analgesic effect in cats in an experimental thermal antinociceptive model at doses ranging from 5 to 30 mg/kg.\textsuperscript{31} However, gabapentin is not expected to be efficacious in preventing acute pain, therefore the lack of effects in this experimental study do not extrapolate to lack of efficacy for clinical use in cats.

Case reports have suggested that gabapentin produced desirable effects in managing trauma and orthopedic pain in cats.\textsuperscript{32,33} Because these were case reports, positive and negative controls were not included. Case studies have been published in dogs suggesting efficacy as an anticonvulsant when combined with phenobarbital and bromide.\textsuperscript{34,35}

No controlled clinical trials have been published evaluating the efficacy of gabapentin as an analgesic or anticonvulsant in dogs or cats, therefore the evidence for its use is low. However, some reports of postoperative use in dogs suggested it was not effective.\textsuperscript{36,37} Because inappropriate dosages (5–10 mg/kg every 12 hours) were used, meaningful conclusions could not be drawn from these studies.

Adverse effects of gabapentin can include sedation and ataxia and are more likely when administered at higher dosages or when combined with other drugs that produce similar adverse effects. Abrupt discontinuation after chronic administration of gabapentin may result in withdrawal and seizures. It is suggested to taper the dose over the course of 1 week when discontinuation of chronic administration is needed. Although the oral liquid formulation contains xylitol, which can be toxic to dogs, the concentration in the solution is low enough that routine dosing of gabapentin is unlikely to result in xylitol toxicity. However, administering multiple products containing xylitol may increase the potential for xylitol toxicity.

The overall evidence for gabapentin use as an analgesic in dogs and cats is low. Pharmacokinetic studies suggest dosages of 10 to 20 mg/kg every 8 hours for dogs and cats. However, there are no controlled clinical trials using appropriate doses supporting or refuting the use of gabapentin as an analgesic. The current cost of gabapentin is low.
Pregabalin

Pregabalin is an FDA-approved anticonvulsant and an analgesic for diabetic neuropathy, postherpetic, and fibromyalgia pain in humans. Extralabel use of pregabalin in humans has suggested that it also decreases opiate consumption after surgery and decreases postoperative nausea and vomiting. There are no published studies assessing pregabalin for osteoarthritis pain. There are no veterinary-approved pregabalin formulations. The mechanism by which pregabalin produces anticonvulsant and analgesic effects has not been definitively identified. However, pregabalin does bind to the alpha-2/delta subunit of the voltage-gated calcium channel (similar to gabapentin), decreasing the release of several neurotransmitters including glutamate and substance P.

The pharmacokinetics of pregabalin have been described in the dog, but not in the cat. In most species, pregabalin is eliminated intact in the urine, but approximately 45% of the administered dose is metabolized to N-methyl-pregabalin in the dog. Pregabalin seems to be well absorbed after oral administration to dogs, with a terminal half-life of approximately 7 hours, suggesting that a dosing schedule of every 12 hours may be appropriate, which is an advantage compared with gabapentin.

Sedation and ataxia are potential adverse effects. Abrupt discontinuation in humans can result in withdrawal and seizures. It is suggested to taper the dose over the course of 1 week when discontinuation after chronic administration is required. Visual disturbances including blurred vision have been reported in humans. Peripheral edema unrelated to changes in blood pressure is a reported adverse effect in humans. Life-threatening angioedema has also been reported in humans.

Pharmacokinetic studies suggest a dosage of 4 mg/kg by mouth every 12 hours in dogs. No case reports, experimental data, or clinical efficacy data are available in dogs or cats. Therefore the evidence for its use is low in dogs and cats. Pregabalin is a DEA CV drug and has a low to moderate potential for diversion or misuse. The current cost of pregabalin is high.

Codeine

Codeine is an FDA-approved mu opioid agonist for the relief of mild to moderately severe pain in humans. Codeine tablets are available as a sole ingredient or in combination with other drugs, including acetaminophen. Codeine is well absorbed in humans (60% oral bioavailability) and is metabolized to numerous metabolites, with codeine-6-glucuronide, norcodeine, and morphine contributing to opioid effects.

In contrast with humans, the oral bioavailability of codeine in dogs is 4% and morphine was not detected in measurable concentrations. However, codeine-6-glucuronide, which is an active opioid metabolite, was formed in high concentrations and may provide analgesic effects in dogs.

The urinary elimination of codeine was evaluated in cats after administration of 20 mg/kg SC codeine. Norcodeine was identified as the major metabolite in cats, but neither the plasma concentrations nor the elimination half-lives of codeine and norcodeine were reported for cats. Further pharmacokinetic studies of codeine are warranted in cats.

Experimental models using electrical stimulation of tooth pulp in dogs showed that the antinociceptive effect of 2 mg/kg SC codeine was similar to 0.1 mg/kg morphine SC, suggesting that parenteral codeine was a low-potency analgesic with a short duration (2 hours) in dogs. Oral codeine (20 mg/kg) produced depression of hind limb reflexes in dogs with chronic spinal disorders that was similar to morphine 0.5 mg/kg, but it is unclear how the study applies clinically to painful dogs.
Regardless, the analgesic/antinociceptive effects of codeine were low with regard to efficacy and potency compared with parenteral morphine. There are no reports of oral codeine efficacy in clinical cases or controlled clinical studies. There are no reports of the antinociceptive/analgesic effects of codeine in cats in experimental studies or clinical cases. Therefore the evidence for use of oral codeine in dogs and cats is low. Although codeine dosages have been recommended at 1.1 to 2.2 mg/kg by mouth every 6 to 12 hours, data are lacking to support those recommendations. It is important to remember that codeine formulations with acetaminophen can be safely administered to dogs, but result in acetaminophen toxicity in cats. Therefore only codeine formulations that do not contain acetaminophen should be used in cats. Codeine as a sole ingredient is a DEA CII drug and combinations of codeine with acetaminophen are CIII drugs. Codeine formulations have a high potential for diversion or misuse. The current cost of oral codeine formulations is low.

**Hydrocodone**

Hydrocodone is a mu opioid agonist that is FDA approved as an antitussive and analgesic in humans. Hydrocodone is only available as combination products, which is likely to curb its potential for abuse. The drug combinations that can be administered to dogs include hydrocodone with homatropine and hydrocodone with acetaminophen. The drug combination that can be administered to cats is hydrocodone with homatropine.

Hydrocodone pharmacokinetics have been reported in dogs dosed with the commercially available hydrocodone/acetaminophen tablets. Oral administration of hydrocodone, 0.5 mg/kg by mouth, resulted in plasma concentrations of hydrocodone and hydromorphone (a hydrocodone metabolite) that persisted for at least 8 hours at concentrations greater than those considered therapeutic in humans. Tablets can be quartered with reasonable accuracy within 22% of the expected hydrocodone content, whereas half-tablet fractions were within 10% of the expected content.

There have been no reported experimental studies or clinical trials evaluating the efficacy of oral hydrocodone in dogs or cats. Hydrocodone is currently a DEA CIII drug and has a high potential for diversion or misuse. The current cost of hydrocodone combinations is low.

**TCAs**

TCAs such as amitriptyline are considered first-line therapeutics for neuropathic pain in humans. Their efficacy has been shown primarily in patients with postherpetic neuralgia. Additional studies have indicated likely efficacy in central neuropathic pain conditions such as poststroke pain, but not spinal cord injury. TCAs were not superior to placebo for rheumatoid arthritis, but were superior to placebo for ankylosing spondylitis and chronic low back pain.

TCAs produce analgesia through multiple mechanisms. They produce serotonin and norepinephrine reuptake inhibition, NMDA antagonism, and voltage-gated sodium channel blockade; they enhance the activity of adenosine and GABAB receptors; and they have antiinflammatory effects. Amitriptyline is the TCA most consistently reported to produce analgesic effects in human neuropathic pain.

Adverse effects of TCAs are primarily caused by their effects as muscarinic antagonists, antihistamines, and alpha-1 antagonists. As such, adverse effects such as xerostomia, polyuria, polydipsia, urine retention, blurred vision (antimuscarinic), sedation (antihistamine), hypotension (alpha-1 antagonism) can occur with TCAs. In humans, weight gain, seizures, agitation, and cardiac arrhythmias can occur. TCAs
have not been associated with GI ulceration. In contrast with SNRIs, TCAs have not been reported to affect platelet function. TCAs have been associated with bone marrow suppression including agranulocytosis, leukopenia, and thrombocytopenia.

The pharmacokinetics of oral amitriptyline were recently reported in dogs. The pharmacokinetics after a dose of 3 to 4 mg/kg resulted in a peak concentration of 126 ng/mL at 2 hours and a short half-life of 5 hours. The active metabolite, nortriptyline, was not assessed. The optimum concentrations of amitriptyline plus nortriptyline in humans are 60 to 220 ng/mL, suggesting that the dose of 3 to 4 mg/kg administered every 12 hours may produce targeted concentrations but, again, without studies assessing nortriptyline concentrations in dogs it is difficult to make dosage recommendations. However, these data may indicate that higher doses of amitriptyline may be needed in dogs than are currently recommended (1–2 mg/kg every 12 hours).

Partial pharmacokinetics of oral amitriptyline in cats are reported after 5 mg per cat (1.3–1.4 mg/kg) using a nonspecific immunoassay that measured amitriptyline and any metabolites (active or inactive). A mean maximum plasma concentration (CMAX) of 61 ng/mL was achieved at 2 hours, and that decreased to about 20 ng/mL at 12 hours. Plasma concentrations of a pluronic lecithin organogel formulation of amitriptyline resulted in low and undetectable concentrations, suggesting it was not a reasonable route of administration.

There are no experimental studies or clinical trials assessing the efficacy of TCAs for canine pain. A case series reported the effects of amitriptyline in 3 dogs with suspected neuropathic pain in which 2 of three were reported to be improved. There are no studies or case reports assessing the efficacy of TCAs in feline pain. The currently recommended doses of amitriptyline, 1 to 2.2 mg/kg every 12 hours, may be too low. The current cost of amitriptyline is low.

**SNRIs**

SNRIs such as venlafaxine and duloxetine have analgesic effects in neuropathic and osteoarthritis pain in humans. Duloxetine is FDA approved to treat humans with chronic low back pain and chronic osteoarthritis, but may take several weeks to achieve the desired effect.

The pharmacokinetics of venlafaxine have been reported in dogs. Oral administration of 4 mg/kg results in a CMAX of 480 ng/mL at 2 hours after administration, with a terminal half-life of 3 hours. The short half-life suggests at least twice-daily, and maybe every 8 hours, administration is needed. The oral bioavailability is about 50%. The active metabolite, desvenlafaxine is apparently not produced in dogs, therefore, in contrast with humans, pharmacologic effects are only caused by the parent drug, venlafaxine. The pharmacokinetics of venlafaxine have not been reported in cats.

Some pharmacokinetic parameters of duloxetine in dogs have been reported as part of the human drug approval by the European Medicines Agency. The oral bioavailability of duloxetine is only 5% in dogs and the terminal half-life is about 4 hours. Although dose-proportional pharmacokinetics are reported up to 30 mg/kg, the plasma concentrations or CMAX were not reported. During toxicology studies, vomiting was dose related and the dose-limiting effect, but other adverse effects such as anorexia, abnormal stools, and mydriasis were reported. Hepatic changes occurred in dogs treated with 30 mg/kg, including microsomal induction (which may further shorten the half-life) and increased liver weight. The unfavorable pharmacokinetic profile of duloxetine favors venlafaxine for further assessment in dogs at this time. The pharmacokinetics of duloxetine have not been reported in cats.
There are no studies reporting the pharmacodynamics effects of venlafaxine or duloxetine in dogs or cats using experimental models, clinical cases, or controlled clinical trials. The cost of the SNRIs are currently much greater than the cost of amitriptyline.

**Glucosamine and Chondroitin**

Glucosamine and chondroitin are nutritional supplements that are anecdotally recommended for use in patients with osteoarthritis. The purported mechanism of action is to support cartilage matrix production and minimize cartilage degradation. There are currently no FDA-approved formulations of glucosamine or chondroitin for dogs or cats.

There has been only 1 published clinical trial incorporating both positive and negative controls that evaluated the efficacy of glucosamine and chondroitin supplements in dogs. Compared with placebo, no significant effects could be attributed to glucosamine and chondroitin, but significant improvements were shown for both carprofen and meloxicam.

Current literature does not support the use of glucosamine and chondroitin supplements for the control of osteoarthritis pain in dogs.

**Morphine, Oxycodone, Methadone**

The pharmacokinetics of oral morphine, oxycodone, and methadone have been reported in dogs. The pharmacokinetics indicate low oral bioavailability and plasma concentrations and short half-lives, suggesting that these opioids do not produce a consistent clinical effect in dogs. Because of the low, variable, and inconsistent absorption of these drugs administered orally in dogs, simple increases in dose are unlikely to produce consistent opioid effects. No studies have reported analgesic effects of oral morphine, oxycodone, or methadone in dogs in either experimental studies or clinical studies.

The pharmacokinetics or analgesic effects of oral morphine, oxycodone, or methadone have not been reported in cats. Because the pharmacokinetics of intravenous administration in cats are similar to those reported in dogs, it is likely these drugs have a low oral bioavailability and lack of consistent clinical effects in cats as well.

Morphine, methadone, and oxycodone are DEA CII drugs and have high potentials for diversion and misuse. The amount of evidence available for these drugs administered orally does not support their use in dogs and cats.

**REFERENCES**


