TOP 5 Pain Medications in Clinical Practice

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Acute pain is a needed process, alerting the body to possible injury. The process starts with the activation of terminal pain receptors, stops once tissue has healed, and usually responds to classic analgesics. Chronic pain, meanwhile, is a prolonged response that is complex and often inappropriate. It does not need the activation of pain receptors to propagate pain; it persists long past the time tissue has healed and can be unresponsive to long-term use of classical analgesics. Injectable medications can be used to manage pain; however, oral medications are a mainstay of chronic pain management for at-home patients. Pain has been traditionally defined as acute or chronic, but more specific terms, including adaptive or maladaptive, are suggested.

1 NSAIDs

NSAIDs act by blocking the cyclooxygenase (COX) enzyme, which drives production of prostaglandins. The COX enzyme has several forms: COX-1, which is responsible for normal body functions; COX-2, which increases in response to inflammation; and, in dogs, COX-3, a third isoenzyme whose action is inhibited by acetaminophen.[1] Specific COX-2–blocking drugs have been developed (deracoxib [Deramaxx, deramaxx.com], firocoxib [Previcox, previcox.us.merial.com]) to decrease adverse effects; however, the role of the various COX forms is more complicated, as COX-2 also contributes to normal body functions.[1] Prostaglandins from both COX-1 and COX-2 have important protective and reparative roles in the GI tract, and prostaglandins from COX-2

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COX = cyclooxygenase, NMDA = *N*-methyl-D-aspartate

Top 5 Pain Medications in Clinical Practice

1. NSAIDs
2. Opioids
3. Anticonvulsants
4. NMDA-receptor antagonists
5. Antidepressants

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regulate renal blood flow. COX-1 can be proinflammatory, whereas the role of COX-3 remains unclear.[1]

Analgesic response varies between individuals; if needed, an alternate NSAID may be helpful after a washout period (dogs, 5–7 days[2]; cats, 2 weeks[3,4]). Adverse effects include GI, renal, and hepatic damage; bleeding; and dermatologic issues.[5-7] The primary cause of adverse effects from NSAIDs is incorrect dosing (eg, concurrent use with corticosteroids or another NSAID, changing NSAID without a suitable washout).[8] Dosing at the lowest effective level (in response to client assessment of pain), maintaining adequate hydration through client education, and drawing blood for frequent tests (ie, chemistry panel 3–4 weeks from initial dose, then q3–6mo depending on risk) can help diminish the incidence of these effects.

The American Association of Feline Practitioners (AAFP) has published guidelines for the chronic use of NSAIDs in cats, reporting that little data are available about feline COX isoenzymes and drug metabolism; these guidelines suggest using a COX-2 selective NSAID, titrating to lowest effective dose and frequency, and dosing based on lean body weight in addition to general guidelines for all species.[9] NSAIDs are highly protein bound and persist in tissue longer than in the bloodstream, so dosing can be less frequent than recommended.[8] NSAID response can improve for up to 12 weeks,[5] partly because of binding in tissue and time needed to decrease nervous system sensitization.[10]

Acetaminophen is a COX-3 inhibitor with a weak effect on COX-1[11] and can be used in dogs (not cats) at 10 mg/kg q12h,[12,13] although its use is not FDA approved. The only NSAID licensed for use in cats in the United States is robenacoxib (Onsior, us.onsior.com), which is FDA approved for 6-day use q24h in oral form; an IV injection can precede this.[9,14] As robenacoxib is in tablet form, compliance may be more challenging than with liquid administration. Meloxicam is used in cats in Canada, and 3–5 day PO administration q24h revealed no significant adverse effects over a 5-day period in adult cats undergoing onychectomy and sterilization.[15] A retrospective analysis of long-term use (>6 months) showed no significant difference in age of mortality between treated and untreated cats with or without chronic kidney disease.[16]

2 Opioids

The analgesic effect of opioids is a result of binding of opioid receptors in the central and peripheral nervous system and GI tract. They decrease perception of and reaction to pain and are effective analgesics. Opioids often have a short half-life in dogs and cats, requiring relatively frequent administration. Also, these medications are FDA controlled, potentially presenting challenges with long-term use. Oral administration of opioids suffers from the first-pass effect of liver metabolism after GI absorption, which can significantly reduce blood levels of the opioid.

Tramadol is an atypical opioid; it has weak μ-opioid action and also acts on the noradrenergic and serotonergic systems.[17] It has been used in both dogs and cats (not FDA approved). In the dog, tramadol is not converted to the active opioid metabolite O-desmethyltramadol in significant amounts, and levels are 10 times lower than those in humans after oral administration.[17,18] In dogs, tramadol is metabolized as N,O-didesmethyltramadol which may have some weak opioid effects; however, repeated doses of tramadol either decreased drug absorption or enhanced presystemic metabolism of tramadol in a previous study.[17]

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International Pain Protocols

A wide variation in pain assessment strategies and management tools exists globally, often resulting in less than optimal treatment. Addressing this deficiency is the WSAVA Global Pain Council, which has recently released the **WSAVA Global Pain Council Pain Management Protocol**. These guidelines directly address such topics as feline and canine ovariohysterectomy and castration, orthopedic and soft tissue surgery, neuropathic pain, and much more.

Find these protocols in upcoming issues of the *Clinician's Brief* Global Edition!

Parenteral administration of tramadol has analgesic effects in dogs,[19,20] likely caused by noradrenergic and serotonergic mechanisms.[21] Oral tramadol has a short half-life resulting in low plasma levels; it should be dosed q6–8h[17,22] and has poor analgesic effect.[17,18,23] In cats, tramadol is converted to the active opioid-binding metabolite and has a longer half-life.[24]

When administered in cats, oral buprenorphine is absorbed transmucosally,[20] provides good analgesia, and is dosed q6h.[25]

3 Anticonvulsants

Gabapentin has analgesic properties and works by inhibiting calcium flow to halt release of excitatory neurotransmitters, although the mechanism of analgesia is not completely understood.[26,27] Whereas gabapentin is frequently used for chronic pain in dogs and cats,[28,29] such use is off label. Studies evaluating the efficacy of gabapentin have focused on short-term (or acute) pain management and have shown little positive effect.[17, 29-31] A case study of neuropathic pain in a dog showed clinical improvement with gabapentin,[32] and long-term use for chronic pain in cats has been reported.[33,34] In dogs, the drug is rapidly absorbed and eliminated; dosing is recommended q8h.[35] The drug is used for seizure management in both the dog and cat. The author starts at an initial lower dose and increases to an adequate established analgesic dose; it is given 2–3 times daily, depending on client compliance. Dogs show some liver metabolism of gabapentin, but the drug is excreted mainly through the kidneys.[36,37] Side effects reported in humans include weakness, drowsiness, blurred vision, and tremor (rarely ataxia).[38] Anecdotal adverse effects include loose stools, weakness, and ataxia. Weakness is usually transient and is the reason the initial dose is low; the author then increases the dose every 2–3 days as the patient adapts. Gabapentin has been combined with opioids and NSAIDs.[28,29]

4 NMDA-receptor antagonists

N-methyl-D-aspartate (NMDA) receptors play an important role in CNS sensitization to pain. Antagonist medications reduce sensitization. Oral administration of amantadine (an NMDA-receptor antagonist) with meloxicam (an NSAID) has been shown to improve pain in dogs.[39] Clients should be advised that, because amantadine needs to reduce CNS sensitivity, it may take several weeks for maximum effect. Safety studies have not been reported; however, daily dosing of dogs with 50 mg/kg for 30 days showed no mortality.[17] Side effects in humans are minor GI disturbances, dizziness, and drowsiness.[13] Use of amantadine in dogs is off label.

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Amitriptyline has been combined with opioids and NSAIDs for management of chronic pain.

5 Antidepressants

Tricyclic antidepressants, mainly amitriptyline, are used to treat chronic pain.[40] Amitriptyline has been used as an adjunctive analgesic in dogs[17] and for interstitial cystitis in cats.[41] Amitriptyline blocks NMDA-receptor antagonists, interacts with opioid receptors, and blocks sodium channels.[38] Side effects of amitriptyline in humans include elevated heart rate, constipation, and sedation.[42] Clomipramine is another tricyclic antidepressant[13] that may be applicable for pain management, but it can be more costly. Amitriptyline has been combined with opioids and NSAIDs for management of chronic pain.[42]

Selective serotonin reuptake inhibitors (SSRIs) are generally considered less effective in managing pain than tricyclic antidepressants, and although SSRIs have fewer reported adverse effects, they can still cause decreased appetite, nausea, drowsiness, and increased heart rate.[43] Use with tramadol should be avoided, as both boost serotonin levels. Fluoxetine is commonly used in human pain management and has been shown to block nerve sodium channels in addition to increasing serotonin.[42] The author has used it successfully for pain in chronically disabled dogs with a reduced quality of life, and it is useful in cats as well. ■ cb

See **Aids & Resources**, back page, for references & suggested reading.

Find More

See the **WSAVA Guidelines for Recognition, Assessment, & Treatment of Pain** by the WSAVA Global Pain Council Members at **onlinelibrary.wiley.com/doi/10.1111/jsap.12200/full** (open access).

NMDA = *N*-methyl-D-aspartate, SSRI = selective serotonin reuptake inhibitor

Meloxidyl®
(meloxicam)

ANADA 200-550, approved by the FDA.
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Meloxidyl®
(meloxicam) 1.5 mg/mL Oral Suspension

Non-steroidal anti-inflammatory drug for oral use in dogs only

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Indications: Meloxidyl Oral Suspension is indicated for the control of pain and inflammation associated with osteoarthritis in dogs.

Contraindications: Dogs with known hypersensitivity to meloxicam should not receive Meloxidyl Oral Suspension. **Do not use Meloxidyl Oral Suspension in cats. Acute renal failure and death have been associated with the use of meloxicam in cats.**

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. See Contraindications, Warnings, and Precautions for detailed information.

Warnings: Not for use in humans. Keep this and all medications out of reach of children. Consult a physician in case of accidental ingestion by humans. **For oral use in dogs only.**

As with any NSAID all dogs should undergo a thorough history and physical examination before the initiation of NSAID therapy. Appropriate laboratory testing to establish hematological and serum biochemical baseline data is recommended prior to and periodically during administration. Owner should be advised to observe their dog for signs of potential drug toxicity and be given a client information sheet about Meloxidyl Oral Suspension.

Precautions: The safe use of Meloxidyl Oral Suspension in dogs younger than 6 months of age, dogs used for breeding, or in pregnant or lactating dogs has not been evaluated. Meloxicam Oral Suspension is not recommended for use in dogs with bleeding disorders, as safety has not been established in dogs with these disorders. As a class, cyclo-oxygenase inhibitory NSAIDs may be associated with gastrointestinal, renal and hepatic toxicity. Sensitivity to drug-associated adverse events varies with the individual patient. Dogs that have experienced adverse reactions from one NSAID may experience adverse reactions from another NSAID. Patients at greatest risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with existing renal, cardiovascular, and/or hepatic dysfunction. Concurrent administration of potentially nephrotoxic drugs should be carefully approached. NSAIDs may inhibit the prostaglandins that maintain normal homeostatic function. Such antiprostaglandin effects may result in clinically significant disease in patients with underlying or pre-existing disease that has not been previously diagnosed. Since NSAIDs possess the potential to induce gastrointestinal ulcerations and/or perforations, concomitant use with other anti-inflammatory drugs, such as NSAIDs or corticosteroids, should be avoided. If additional pain medication is needed after administration of the total daily dose of Meloxidyl Oral Suspension, a non-NSAID or non-corticosteroid class of analgesia should be considered. The use of another NSAID is not recommended. Consider appropriate washout times when switching from corticosteroid use or from one NSAID to another in dogs. The use of concomitantly protein-bound drugs with Meloxidyl Oral Suspension has not been studied in dogs. Commonly used protein-bound drugs include cardiac, anticonvulsant and behavioral medications. The influence of concomitant drugs that may inhibit metabolism of Meloxidyl Oral Suspension has not been evaluated. Drug compatibility should be monitored in patients requiring adjunctive therapy.

Adverse Reactions: Field safety was evaluated in 306 dogs. Based on the results of two studies, GI abnormalities (vomiting, soft stools, diarrhea, and inappetance) were the most common adverse reactions associated with the administration of meloxicam. The following table lists adverse reactions and the numbers of dogs that experienced them during the studies. Dogs may have experienced more than one episode of the adverse reaction during the study.

In foreign suspected adverse drug reaction (SADR) reporting over a 9 year period, incidences of adverse reactions related to meloxicam administration included: auto-immune hemolytic anemia (1 dog), theromabocytopenia (1 dog), polyarthritis (1 dog), nursing puppy lethargy (1 dog), and pyoderma (1 dog).

Adverse Rections Observed During Two Field Studies

Clinical Observation	Meloxicam (n=157)	Placebo (n=149)
Vomiting	40	23
Diarrhea/Soft Stool	19	11
Bloody Stool	1	0
Inappetantance	5	1
Bleeding Gums After Dental Procedure	1	0
Lethargy/Swollen Campus	1	0
Epiphora	1	0

Post-Approval Experience: (Rev 2010)
The following adverse events are based on post-approval adverse drug experience reporting. Not all adverse reactions are reported to FDA/CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data. The following adverse events are listed in decreasing order of frequency by body system.

Gastrointestinal: vomiting, anorexia, diarrhea, melena, gastrointestinal ulceration
Urinary: azotemia, elevated creatinine, renal failure
Neurological/Behavioral: lethargy, depression
Hepatic: elevated liver enzymes
Dermatologic: pruritus

Death has been reported as an outcome of the adverse events listed above. **Acute renal failure and death have been associated with use of meloxicam in cats.**

Effectiveness: The effectiveness of meloxicam was demonstrated in two field studies involving a total of 227 dogs representing various breeds, betweens six months and sixteen years of age, all diagnosed with osteoarthritis. Both of the placebo-controlled, masked studies were conducted for 14 days. All dogs received 0.2 mg/kg on day 1. All dogs were maintained on 0.1 mg/kg oral meloxicam from days 2 through 14 of both studies. Parameters evaluated by veterinarians included lameness, weight-bearing, pain on palpation, and overall improvement. Parameters assessed by owners included mobility, ability to rise, limping, and overall improvement. In the first field study (n= 109), dogs showed clinical improvement with statistical significance after 14 days of meloxicam treatment for all parameters. In the second field study (n = 48), dogs receiving meloxicam showed a clinical improvement after 14 days of therapy for all parameters; however, statistical significance was demonstrated only for the overall investigator evaluation on day 7, and for the owner evaluation on day 14.

How Supplied: Meloxidyl® 1.5 mg/mL Oral Suspension: 10, 32, 100 and 200 mL bottles with small and large dosing syringes.

Storage: Store at controlled room temperature 68-77° F (20-25° C).
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