PRACTICAL PHARMACOLOGY

Select Drugs and Compounds for Canine Osteoarthritis Management

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Osteoarthritis (OA) is the most common cause of chronic pain in mammals. It is considered an end-stage disease because there is no cure. While mild to moderate acute pain is "adaptive" or "physiologic" and has biological value in that it is primarily linked to the inflammatory phase of healing after tissue injury, chronic pain is "maladaptive" or "pathologic," meaning that it is not linked to a healing phase and often comes from sources other than injury or from a disease that will not heal, like OA. Thus, chronic pain has no biological value or purpose.

Pain, acute or chronic, can cause moderate to profound changes in a patient's health, behavior, welfare, and quality of life. When left untreated, pain continues to generate and escalate through the processes of peripheral and central sensitization. Unfortunately, many animals with chronic pain go untreated, either because they are extremely adept at hiding pain or because the behavioral signs of pain are misidentified by caregivers as animals "just getting old."

The number of therapeutics available for OA pain in dogs is slowly growing, and new options include treatments with novel mechanisms of action. Existing therapeutics are also very important for effective analgesia, although there are often misconceptions regarding their use and, other than nonsteroidal anti-inflammatory drugs (NSAIDs), few are robustly studied. This article includes information on both newly released and most commonly used existing options for the treatment of OA pain in dogs.

Abstract

Osteoarthritis pain can be difficult to treat, but newer drugs and compounds, and some existing ones, can be used effectively either alone or as part of multimodal therapy. Newer therapies include those with unique mechanisms of action, intra-articular compounds, and unique combinations of normal joint compounds. The introduction of new therapies is exciting; however, reliance on existing drugs, many with minimal evidence of efficacy, is still heavy. Thus, more approved analgesic drugs and new compounds for treatment of osteoarthritis pain in dogs would be a welcome advancement. This review covers both new and commonly used existing drugs and compounds for control of osteoarthritis pain in dogs.

Take-Home Points

- Osteoarthritis (OA) can be very difficult to treat and may require multimodal therapy, depending on the degree of pain and treatments available.
- Newer therapies include those with novel mechanisms, such as anti–nerve growth factor (NGF) monoclonal antibodies (mAbs); intra-articular compounds, such as radioactive tin; and unique combinations of normal joint compounds like collagen.
- Many existing drugs are used anecdotally for the treatment of OA pain in dogs and are still important parts of therapy due to a lack of options, but research on these drugs is sparse and their use is primarily predicated on a known mechanism of action that should provide analgesia.
- Among current systemic options, the anti-NGF mAbs and nonsteroidal anti-inflammatory drugs provide the most potent, predictable analgesia with the longest dosing interval and should be considered a first-line option for treatment of OA pain in dogs to both provide analgesia and decrease caregiver burden by limiting treatment frequency.
- The new intra-articular injections could potentially also be considered as a first-line option in some patients.

Unfortunately, there have been few to no new publications on most of the existing drugs. Nonpharmacologic treatments are also an important component of OA pain control but are outside the scope of this article. An in-depth guideline on treatment of both acute and chronic pain has been recently published.[1]

Although tramadol is sometimes prescribed for canine OA, studies have demonstrated that this drug has no effect for control of OA pain in dogs, likely because dogs do not make the opioid metabolite that would provide opioid-level analgesia. Some effect from the serotonin–norepinephrine reuptake inhibition may provide pain relief in individual dogs; however, tramadol is also a U.S. Drug Enforcement Administration (DEA) Schedule IV drug that is known to be diverted for human abuse, thus complicating its dispensing. Tramadol is therefore not recommended in this article as a routine therapy for OA pain in dogs.

SYSTEMICALLY ADMINISTERED DRUGS

NEW: Anti–Nerve Growth Factor Monoclonal Antibody (Bedinvetmab; Librela)

Approval status: Approved by the U.S. Food and Drug Administration (FDA) in May 2023; approved in Canada (2023) and various other countries starting in 2020

Manufacturer: Zoetis (zoetis.com)

Mechanism of action: The anti–nerve growth factor (NGF) monoclonal antibody (mAb) targets and neutralizes the NGF, thus decreasing the amount of free NGF available for binding to the tyrosine kinase A receptors located on neurons and immune cells. NGF is a potent pain generator and propagator that is overexpressed in osteoarthritic joints.[2]

Indication: The label indication is for the alleviation of pain associated with OA in dogs. Few off-label uses have been explored at this time.

Administration: The recommended dose is 0.5 to 1 mg/kg SC once a month for as long as the patient experiences OA-associated pain. Since OA is not curable, treatment will likely be needed for the rest of the patient's life.

Key clinical data: In 287 client-owned dogs with OA, bedinvetmab produced a significant effect over placebo on pain interference, pain severity, and quality of life. Minor adverse health events occurred in both groups and were determined to be predictable for the population and not related to study treatment.[3]

Most common side effects: Mild reactions at the injection site in ≤1% of dogs

Clinical use: Based on its mechanism of action, proven efficacy, and wide safety margin, bedinvetmab should be a first-choice drug for OA pain.[1] The need for multimodal therapy has not been evaluated, but NSAIDs have been safely coadministered for 2 weeks.[4]

NSAIDs

Approval status:: Carprofen (1996), deracoxib (2002), meloxicam (2003), firocoxib (2004), grapiprant (2016) are all U.S. FDA approved.

Manufacturer: Carprofen, deracoxib, meloxicam, and firocoxib have various manufacturers, including parent drugs and generics. Grapiprant is manufactured by Elanco (elanco.com).

Mechanism of action: All except for grapiprant block cyclooxygenase (COX) 1 and 2 enzymes in the arachidonic acid pathway. Grapiprant blocks the prostaglandin E receptor 4 (EP4) receptor rather than the production of prostaglandins. Since EP4 receptor blockade occurs lower in the arachidonic acid pathway than blockade of COX enzymes, the homeostatic roles of the COX enzymes are spared.

Indication: OA pain relief

Administration: All are q24h PO (carprofen is also approved for q12h dosing with half the total dose administered at each time). Some products also have an injectable formulation for in-hospital use, if needed.

Key clinical data: All listed NSAIDs have both efficacy and safety studies supporting their use. Few to no studies directly compare 1 NSAID to similar NSAIDs. Individual animal sensitivities to analgesic effects and adverse effects are expected as there are individual variations in response. Grapiprant may have a higher safety profile, and potentially lower efficacy in some situations, due to its targeted mechanism of action.[5,6]

Most common side effects: The most common adverse effect is gastrointestinal upset (e.g., vomiting, diarrhea). Gastrointestinal ulceration and renal and hepatic adverse effects are less common; their incidence is unknown, but likely low.[1]

Based on their mechanism of action and proven efficacy, NSAIDs should be first-choice drugs for OA pain.[1]

Key point: Longer-duration treatment often improves efficacy and is unlikely to increase the incidence of adverse effects.[1]

Clinical use: Based on their mechanism of action and proven efficacy, NSAIDs should be first-choice drugs for OA pain.[1] NSAIDs are commonly used as part of a multimodal protocol in patients with moderate to severe pain.

Polysulfated Glycosaminoglycan (Adequan Canine)

Approval status: U.S. FDA approved (2014) as a disease-modifying OA drug

Manufacturer: American Regent Animal Health (aranimalhealth.com)

Mechanism of action: The full mechanism of action is not completely elucidated, but this drug has been shown to inhibit some catabolic enzymes that have increased activity in inflamed joints. Other mechanisms include increased synthesis of proteoglycan and hyaluronic acid. These mechanisms are predicted to potentially decrease intra-articular cartilage loss (i.e., "disease modifying"), thus providing analgesia.[7]

Indication: The label states, "Control of signs associated with noninfectious degenerative and/or traumatic arthritis of canine synovial joints."

Administration: The recommended label dose is 4.4 mg/kg body weight (0.009 mL/kg or 1 mL per 22.7 kg) IM twice weekly for up to 4 weeks (maximum of 8 injections). Clinically, this course of injections is often repeated "as needed" to control the patient's pain.

Key clinical data: Data from a controlled field trial showed a treatment-related statistically significant improvement in range of motion and total orthopedic score (i.e., lameness at walk and trot, disability, pain).[8] Few publications exist, with the most recent showing that subcutaneous administration caused infrequent, minor, and mostly self-limiting adverse effects (e.g., stomach "upset," bruising at the injection site) according to dog owners.[9] No other data were reported.

Most common side effects: Mild and self-limiting transient pain at the injection site, transient diarrhea, and bruising

Clinical use: In most dogs, unless OA is very mild, the product is most effectively used as part of a multimodal strategy and/or to replace oral drugs in dogs that are unwilling or unable to take oral medication (due to contraindications or difficulty medicating).

Gabapentin/Pregabalin

Approval status: No approval for veterinary use in the United States

Manufacturer: Various parent and generic formulations

Mechanism of action: The primary mechanism is presynaptic inhibition of calcium channels (specifically the α-2-Δ-1 subunit), resulting in decreased calcium influx with decreased release of excitatory neurotransmitters. Anxiolytic effects can also decrease pain intensity.[10]

Indication: Potential adjunctive drug for chronic pain relief[1]

Administration: Dosing recommendations are primarily anecdotal.

- **Gabapentin:** q8h to q12h PO (q8h is generally most recommended based on pharmacokinetics data). Starting dose is 10 mg/kg, potentially up to 40 mg/kg.[11,12] Gabapentin undergoes more hepatic than renal clearance in dogs compared to cats; thus, the dose reduction recommended for cats with renal disease is not generally necessary in dogs.
- **Pregabalin:** 1 to 2 mg/kg PO q12h. An oral dose of 4 mg/kg was shown to provide serum concentrations predicted to prevent seizures, but pain relief was not discussed in this study.[13]

Key clinical data: Few studies are available for gabapentin, and only case reports are available for pregabalin. Because gabapentin is not a potent analgesic, results are mixed and most studies are based on dosages or dosing intervals lower than those expected to provide an analgesic effect.[14] In 32 dogs with neuropathic pain, gabapentin administered at 10 mg/kg PO q8h with or without meloxicam reduced pain scores compared with presentation baseline.[15] Pregabalin relieved neuropathic pain from syringomyelia.[16] Although these studies are not specific to OA, OA pain is often considered to be a type of neuropathic pain.[10]

Most common side effects: Sedation, which usually resolves within a few days and can be used as an advantage by increasing evening dose so that the patient sleeps through the night. Ataxia, more common in large dogs, may resolve with decreased dosing.

Clinical use: Gabapentin or pregabalin is used as a component of a multimodal protocol in patients with pain that is difficult to control or when more potent drugs are not available or contraindicated.[1] Compared to gabapentin, pregabalin has greater affinity for the voltage-gated calcium channel on the presynaptic membrane, which may lead to greater analgesic efficacy.[17] In addition, pregabalin has faster oral absorption as well as linear pharmacokinetics in humans and presumed linear pharmacokinetics in dogs.[17] This leads to more predictable dose-related effects. Pregabalin is a DEA Schedule IV controlled drug in the United States, and gabapentin is a DEA Schedule IV controlled drug in some U.S. states.

NMDA-Receptor Antagonists (Amantadine, Ketamine)

Approval status: Amantadine is not approved for veterinary use in the United States. Ketamine is approved as an injectable anesthetic drug in cats and subhuman primates in the United States.

Manufacturer: Various parent and generic formulations

Mechanism of action: *N*-methyl-D-aspartate (NMDA) receptors in the spinal cord are generally plugged with magnesium, but the magnesium plug can be extruded when depolarization of the postsynaptic membrane occurs after activation of other glutamate receptors, such as AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors. NMDA-receptor antagonists can take the place of the magnesium to plug the channel, which decreases the occurrence of central sensitization.

Indication: Potential adjunctive drug for acute or chronic pain relief, particularly if central sensitization is predicted to be a component of pain.[1] Chronic and/or severe OA pain can lead to central sensitization.

Administration: Dosing recommendations are primarily anecdotal.

- **Amantadine:** 3 to 5 mg/kg PO q12h to q24h (q12h generally more effective)

- **Ketamine:** No published data exist in veterinary medicine for use in chronic pain, but this drug is fairly commonly used in human medicine.[18] There are no standard protocols for ketamine use in relief of OA pain in dogs, but the acute infusion dose (approx. 5 to 10 µg/kg/min) is often used for 4 to 24 hours to decrease central sensitization. 0.5 mg/kg SC weekly or less often (or more often for severe pain) has also been used with some success in the author's experience.

Key clinical data: Amantadine added to an NSAID increased activity level in dogs with OA.[19] Ketamine administration is used in human medicine to decrease central sensitization in chronic pain states but has not been critically studied in dogs for chronic pain, although efficacy for acute pain has been reported.[20] The Zero Pain Philosophy website (zeropainphilosophy.com) is a good resource for more information on the use of ketamine as an analgesic, including subcutaneous administration.

Most common side effects: Sedation or agitation (rare)

Clinical use: NMDA-receptor antagonists can be used as a component of a multimodal protocol in patients with pain that is difficult to control.[1] Ketamine is a DEA Schedule III drug in the United States. Amantadine is contraindicated for animal use in some countries due to its antiviral properties and the concern for development of resistant virus strains.

INTRA-ARTICULARLY ADMINISTERED MEDICAL DEVICES

NEW: Homogeneous Tin Colloid (^{117m}Sn; Synovetin OA)

Designation: Medical veterinary device

Manufacturer: Exubrion Therapeutics, Inc. (synovetin.com)

Mechanism of action: The injected tin colloid emits low-energy conversion electrons that are absorbed by synovial cells and macrophages, causing apoptosis, resultant reduction of inflammatory cells, and decreased synovial inflammation and pain.

Indication: The label indication is for intra-articular treatment of elbows in dogs to reduce synovitis and associated OA pain. The therapy has been used for off-label injection in other joints.

Administration: The label states that dogs must be anesthetized or deeply sedated during injection and that a 22-gauge needle is required. Redosing can be performed no sooner than 12 months after the last treatment, and doses are strictly regulated.

Key clinical data: An elbow injection in 14 dogs with grade 3 elbow OA resulted in significant reduction in pain and lameness and improved functionality in most dogs for up to 1 full year, with no adverse treatment-related effects.[21]

Most common side effects: Pain at the joint during and up to 72 hours after treatment (uncommon)

Clinical use: Injection of elbows (on-label) and other joints (off-label) at approved radiation treatment facilities. Household members of the treated patient must agree to comply with home care instructions that minimize human exposure to radiation emitted from the elbow immediately after treatment. This treatment could be considered for first-line therapy in any dog, including those not able or willing to take oral medications, or as a part of a multimodal protocol.

NEW: Collagen/Elastin Matrix (Spryng)

Designation: Medical veterinary device

Manufacturer: PetVivo Holdings, Inc. (sprynghealth.com)

Mechanism of action: Designed to mimic natural cartilage and restore proper joint mechanics, leading to decreased pain.

Indication: The label states, "To aid in the management of joint pain from loss of cartilage or tissue-bone mechanical malfunction caused by joint dysfunction not associated with infection." The goal is to reinforce natural cartilage.

Administration: Intra-articular sterile injection in joints. Approach to joint, needle size, and amount of injectate are at the veterinarian's discretion. Multiple joints can be injected at the same appointment, and repeat injections can be performed as needed.

Key clinical data: Publications on use in dogs are in progress, with current use based on success in horses.

Most common side effects: Mild, short-term swelling at the injection site

Clinical use: Injection into joints with OA. This therapy could be considered for first-line therapy in any dog, including those not able or willing to take oral medications, or as a part of a multimodal protocol.

SUMMARY

Systemically administered drugs such as the new anti-NGF mAb and existing NSAIDs should be the first-line choices for most dogs with OA pain. These are the best options not only to provide effective analgesia but also to decrease the caregiver burden that can result from administering multiple drugs or multiple daily dosages of less potent drugs. New targeted intra-articular injections are also emerging as potential first-line therapies. Existing drugs with scientifically proven mechanisms, such as NMDA-receptor antagonists and gabapentin/pregabalin, should be considered as adjunctive drugs; however, more research on dosing and dosing intervals specific to dogs is needed and important. The market entry of a few new drugs for treatment of OA pain in dogs is exciting, and more entries are needed. TVP

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