Practical Approach to Pain Management and Rehabilitation in Canine Osteoarthritis

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Dealing with pain is a significant challenge for owners of companion animals and the provider of their medical care. Managing pain goes far beyond the administration of medications. It includes developing a strategy that will increase patient strength and fitness, optimize the pet's body weight, implement a home exercise program, make appropriate use of safe and effective ambulation assistance devices, and optimize the home environment. However, to allow an effective rehabilitation program to be implemented and to achieve optimum results, logical, safe, and effective use of analgesics is required. This therapy must be tailored to the individual animal, should be multimodal, and needs constant reevaluation for efficacy and toxicity.

This practical review covers the drug and non-drug options used in designing a comprehensive management plan in patients with chronic pain associated with osteoarthritis (OA). Non-drug options include cold therapy, heat therapy, massage, stretching, electrical stimulation, therapeutic exercises, and others. Weight management and nutritional strategies used to manage osteoarthritis are reviewed. Ambulation assistive devices and environment modification for osteoarthritic patients are discussed. For most aspects of rehabilitation, such as therapeutic exercise,

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effective analgesia is required. Drug options include nonsteroidal antiinflammatory drugs, or NSAIDs (COX-1 sparing, coxibs, and dual inhibitors), acetaminophen, *N*-methyl-D-aspartate (NMDA) antagonists (amantadine), anticonvulsants (gabapentin), and mixed analgesics (tramadol). The logical and safe use of such drugs is discussed.

INTRODUCTION

Chronic pain probably originates in the joint capsule or joint surface of dogs with chronic osteoarthritis.[1] With the disuse resulting from osteoarthritis, a loss of muscle mass occurs in limbs with osteoarthritic joints.[2,3] With disuse, muscle function is also decreased beyond the loss of function related to that loss of muscle mass. That additional loss of muscle function may be caused by changes in neurophysiology of the muscle contraction and muscle cell physiology associated with lack of use and with a reflex inhibition of muscle contractions.[4] Some think that neurogenic factors may be a primary factor in the development of arthritis in the human knee joint.[5,6] As a result of the loss of muscle mass and function, additional stress is placed on arthritic joints during locomotion, creating additional pain (**Figure 1**). Often, range of motion of joints is decreased in dogs with osteoarthritis due to a variety of factors, including thickening of the joint capsule. Dogs with limited range of motion in their arthritic joints tend to perceive more pain because these joints are functioning near extreme flexion (e.g., with elbow dysplasia) or extension (e.g., with hip dysplasia).

NUTRITION: BODY WEIGHT AND SUPPLEMENTATION

Body weight has a profound impact on OA: being overweight increases the likelihood of developing OA (by a factor 2 to 5 depending on the joints in one study)[7] and it decreases lifespan. Median lifespan decreased by 1.8 years or 14% in overweight dogs in one study.[8] Musculoskeletal problems, particularly OA, were the most common cause of death or euthanasia in that study, and it doubled the need for pain medications over a lifetime.[9] In another study of overweight dogs with OA, losing weight lead to an increase in limb use.[10]

Food supplementation for OA patients may include glucosamine, chondroitin, and omega-3 (n-3) fatty acids. These supplements have been beneficial to OA patients in several clinical trials. In one trial of 38 client-owned dogs with OA, the average improvement was 5.35% of peak vertical force when dogs were fed a food supplemented with n-3 fatty acid, glucosamine, and chondroitin.[11] Eighty-two percent of the dogs receiving the supplement improved versus 31% of the non-supplemented group.[11]

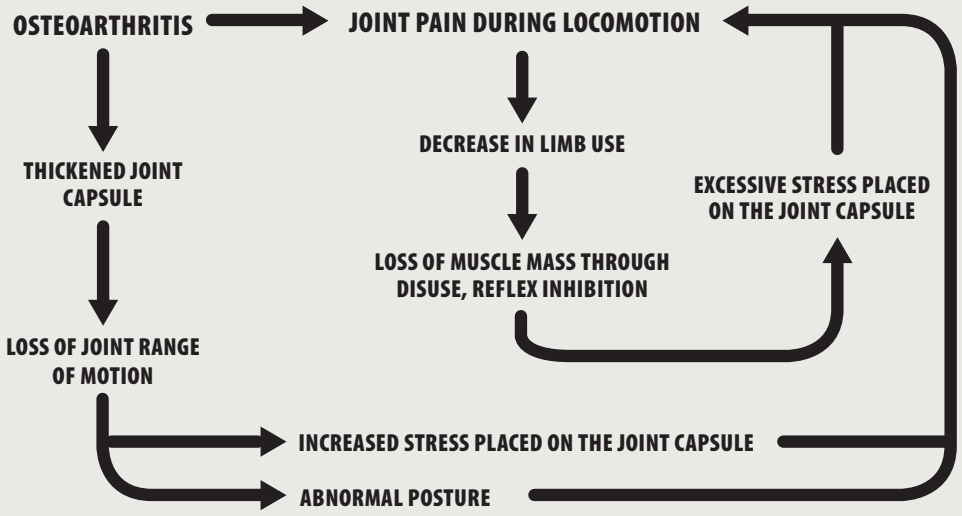

Figure 1. Vicious circles created by osteoarthritis.

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PASSIVE THERAPEUTIC OPTIONS

COLD THERAPY applied to tissue has antiinflammatory and analgesic properties.[12,13] It decreases edema, muscle spasm, and nerve conduction velocity. Cooling a joint below 30°C also decreases cartilage-degrading enzymes.[13,14] Cold is most often applied using frozen gel packs. Cold packs may be home-made by mixing two volumes of water and one volume of isopropyl (rubbing) alcohol in a Ziplok® bag. Cold is used to soothe OA patients when flare-ups occur. It is also used after therapeutic exercise (**Figure 2**).

HEAT THERAPY leads to muscle relaxation potentially because of vasodilation in muscle spasms (regions of hypercontractile muscle fibers).[12,13] The tissues are generally heated by 1 to 2°C (2 to 4°F) for relaxation. Heat also increases collagen extensibility.[15,16] To stretch tissues, heat is applied during or immediately before stretching. Optimal stretching requires an elevation of tissue temperature of at least 3 to 4°C (6 to 8°F) to reach 43 to 45°C (109.4 to 113°F). Heat may be delivered using a moist or dry heat pack, through massage, in warm water, or through therapeutic ultrasound. Moist heat is considered to be more comfortable than dry heat. Moist heat packs may be kept in a hydrocollator at 75°C (165°F) or may be microwaveable. Therapeutic ultrasound is used most often when deep tissue heating is needed. While moist heat packs can elevate tissue temperature to a depth of 3 cm, therapeutic ultrasound can elevate tissue temperature to a depth of 5 cm.

STRETCHING is most often performed immediately after heating. Stretching may benefit OA patients with loss of range of motion. A loss of joint motion may limit limb use and create pain because of the resulting excessive pull on the joint capsule (see Figure 1). Loss of joint motion in OA patients most often results from a thickened, fibrotic joint capsule or from fibrous tissue surrounding the joint capsule. More rarely, loss of joint motion in OA patients may be secondary to sustained muscle spasms or contractures. Stretching of osteoarthritic joints is generally performed using 20- to 40-second-long sustained stretches repeated 10 to 15 times during a stretching session.

MASSAGE has been shown to decrease muscle spasm and increase local blood flow. It may be used to stretch tissue and increase motion between tissue planes. While massage does not have clear benefits in OA patients, it may be used in combination with stretching in patients with limited joint motion and may provide short-term pain relief in OA patients with muscle spasms and tight joints.[17]

Electrical modalities are also used for OA patients. Transcutaneous electrical nerve stimulation (TENS) provides pain relief by stimulating cutaneous pain fibers. TENS is effective through a gate-control or counter-irritant mechanism: a large number of benign stimuli compete with the noxious stimuli originating in and around the arthritic joint. TENS has proven benefits in decreasing pain in OA patients; the optimal treatment duration in people appears to be 40 minutes.[18] Neuromuscular electrical nerve stimulation (NMES) is used for muscle strengthening. NMES has some benefits in OA patients; it may be used to strengthen specific muscles in OA patients with severe joint pain or disuse.[19]

Other passive modalities including joint mobilization,[20,21] acupuncture,[22,23] electro-acupuncture, acupressure, myofascial release, extracorporeal shockwave therapy, and magnet therapy [24,25] are used to manage osteoarthritis.

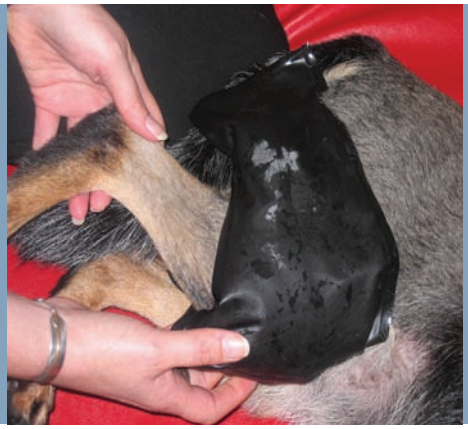

Figure 2. **Rebel, a 7-year-old female Australian Cattle Dog recovering from stabilization after cranial cruciate ligament rupture, receives cold therapy delivered using a gel pack after an exercise session. The gel pack is placed around the stifle joint for 10 minutes.**

Table 1. Therapeutic Exercises Potentially Used in a Veterinary Clinic and at Home

Exercises in Clinics	Similar Home Exercises	Purpose
Underwater treadmill	Leash walk	Limb and core muscle strengthening Increase endurance Increase cardiovascular fitness
Uphill trot on land treadmill	Climb hill	Strengthening pelvic limbs Stretch pelvic limbs in extension
Cavaletti rails	Serpentine curbs*	Stimulate proprioception Promote carpal and tarsal flexion

** Walking up and down a curb in a snake-like manner*

ACTIVE REHABILITATION: THERAPEUTIC EXERCISES

Therapeutic exercises are beneficial to OA patients.[26-28] Exercises increase strength and endurance, stretch tight muscles and joints, and improve posture (**Table 1**).[28] Exercises may be performed with support provided by a sling, a cart, an elastic band, an exercise ball, or water (**Figure 3**). These exercises are called *active assisted exercises*. Exercises may also be performed independently, without external support, and are referred to as *active exercises*. Dogs able to exercise independently should do so. Dogs unable to exercise independently should perform active assisted exercises. Over time, as dogs become stronger and acquire more endurance, the assistance should be decreased.

Figure 3. **Rebel is exercising on a therapy ball. The ball is moved forward and back and side-to-side to safely load her operated limb, to promote a weight shift towards that limb, and to stretch her operated stifle joint.**

The most common exercises used in OA patients include walking (**Figure 4**), walking with resistance provided by water or elastic bands, trotting, climbing slopes, half steps (**Figure 5**), and full steps, walking across Cavaletti rails (**Figure 6**), and sit-to-stand and stand-to-sit exercises (**Figure 7**). Walking is the simplest, most natural, and most fundamental exercise (**Figure 8**). Walking may be endlessly adapted to fit the needs of OA patients, including duration, frequency, intensity, ground surface (asphalt, grass, dirt, muscle, gravel, sand), slope (flat, uphill, downhill—**Figure 9**), and leash or chest harness (Figure 8).

Proprioceptive exercises may be added to the exercise routine of OA patients because a loss of function of proprioceptive joint mechanoreceptors has been identified in aging patients compared with younger patients.[29] A further loss of function has been identified in OA patients.[29,30] Exercises enhance proprioception in humans.[31] Exercises that would stimulate proprioception

Figure 4. **Rebel is exercising on an underwater treadmill. The treadmill is inclined upwards by 8° to increase stifle and hip extension during exercise.**

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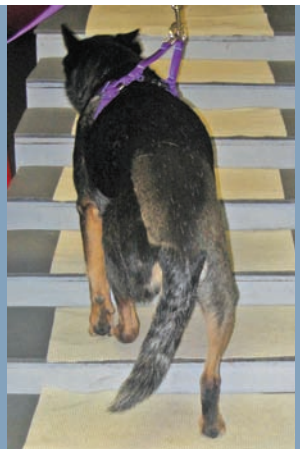

Figure 5.

Rebel is walking up a set of 3-inch-high half steps to strengthen her pelvic limbs and promote stifle and hip joint extension.

Figure 7.

Rebel is performing a stand-to-sit exercise that will strengthen her hind limbs.

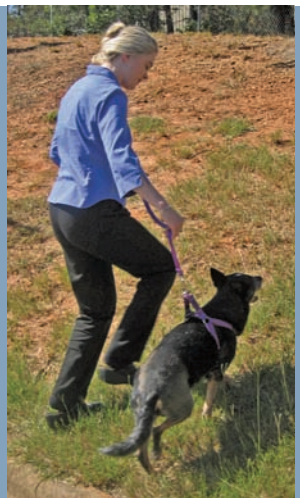

Figure 9.

Rebel is climbing a hill, this outdoor exercise is similar to climbing half steps (see Figure 5).

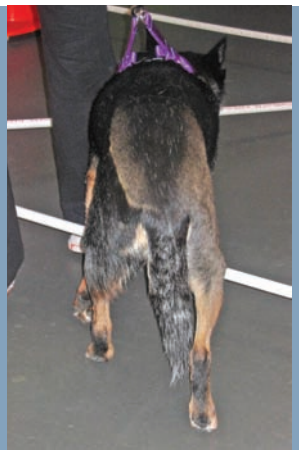

Figure 6.

Rebel is walking across oblique Cavaletti rails to promote stifle joint flexion, to promote an even weight distribution, and to stimulate her hind limb proprioception.

Figure 8.

Rebel is exercising outside on a leash. The leash is connected to a chest harness to increase the control of her posture and weight distribution.

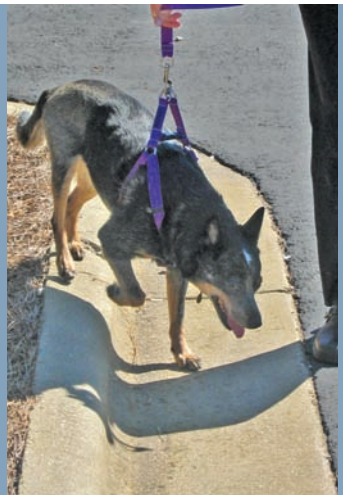

Figure 10.

Rebel is exercising outside using a 'serpentine curb' pattern. She is asked to climb up and down a curb while walking alongside to promote weigh shifting and mildly increase the propulsive role of her pelvic limbs.

include exercises performed on soft and irregular surfaces and exercises that require changing direction and speed. These exercises include walking on grass, mulch, gravel, dirt, or sand, walking on and off a curb (**Figure 10**), walking in circles or figure-of-eight, walking across Cavaletti rails, and walking on a wobble or balance board.

The exercise program in the rehabilitation clinic and at home should be customized to the patient, its medical problems, its owner, and its environment. The patient's personality, size, body condition score, and fitness level are important factors in designing an exercise program. The severity of the problems, their chronicity, the owner's ability and willingness to get involved in the patient's therapy, and the dog's surroundings (urban versus rural, hot versus cold climate, etc.) are other important factors. The exercise program is often initiated in the clinic and conducted there in the short term (see Figures 2 to 7; Table 1). Exercise may also be performed under the supervision of the owner, at home or outdoors (Figures 8 to 10; Table 1). While specialized equipment and specific knowledge and experience in the clinic facilitate the implementation of an exercise program, many exercises may be simplified, adapted, and performed by the owner (Table 1). To be effective in a home exercise program, the owner has to assess the patient during and after exercise periods.

USING AMBULATION ASSISTANCE DEVICES

Severely affected OA patients may benefit from the support provided by slings, orthotics, braces, or ambulation carts (**Table 2**). Rubberized or neoprene slings may be used to support OA patients with loss of strength. Slings are most often placed around the caudal aspect of the abdomen to support patients with weak pelvic limbs. Orthotics are external structures placed on the limbs to support or protect these limbs; they are generally placed around weak extremities (i.e., carpus and tarsus). Braces are external structures places on limb segments and joints that may decrease instability or place specific torque on joints. Braces are most often used on elbow and stifle joints. Ambulation carts may be used temporarily or permanently to help weak and painful patients. In patients with problems affecting their lower back and pelvic limbs, carts with two wheels are generally used. In patients with problems affecting their forelimbs or all limbs, carts with four wheels are generally used.

OPTIMIZING THE HOME ENVIRONMENT

OA patients benefit from modifications of their daily environments (**Table 3**). These modifications are aimed at decreasing the amplitude of temperature and barometric changes sustained by OA patients, increasing the traction offered by walking surfaces, decreasing the need to jump up or down, decreasing the need to climb up or down long sets of stairs, decreasing the efforts needed to eat and drink, and increasing the comfort of sleeping surfaces. The environmental changes often implemented in OA patients include having access to a ramp to climb up and down to get in and out of motor vehicles and to climb challenging

Table 2. Ambulation Assistive Devices Used for Osteoarthritis Patients

Device	Benefits	Potential Candidates
Harness	Decrease stress on neck region Light support of forequarters	Wobbler syndrome
Neoprene sling	Moderate support of fore- or hind quarters	Severe hip dysplasia
Brace	Limit joint motion Decrease stress placed on joints	Cranial cruciate ligament injury
Orthotic device	Eliminates joint instability Decrease joint pain	Carpal hyperextension
Elastic bands*	Decrease ataxia Facilitate hock flexion	Lumbo-sacral disease
Ambulation cart	Complete support of hind quarters	Bilateral hip luxation

** Specialized bands connecting proximal portion of the metatarsal bones to shoulder region.*

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Table 3. Environmental Modifications Beneficial to Osteoarthritis Patients

Feature	Before Modification	After Modification
Food and water	At ground level	Food and water are elevated
Walks	Dog walks on hard surfaces	Dog walks on soft surfaces
	'Week-end warrior'	Dog exercises regularly
Home entry / exit	Steps, may be slippery	Ramp with non-skid surface
Floor surface	Slippery floors	Area rugs
Bedding	Hard bedding Sleeping outdoors	Comfortable bed Avoid wide temperature and humidity swings
Car rides	Dog jumps into the car Car access is difficult	Dog uses dog ramp Vehicle is lower and has comfortable entry

sets of steps, having indoor carpeted surfaces, having elevated food and water bowls, and sleeping indoors.

DRUG THERAPY TO FACILITATE PAIN-FREE REHABILITATION

In order to facilitate rehabilitation exercises and to optimize the beneficial effects of rehabilitation therapy, effective analgesia is required. The first line of drugs usually selected are the nonsteroidal anti-inflammatory drugs (NSAIDs)—cyclooxygenase-1 (COX-1) sparing, selective COX-2 inhibitors, or coxibs, and dual inhibitors. NSAIDs are an appropriate first choice, and we are fortunate to have a number of approved drugs available, allowing us to change drugs to optimize individual efficacy and decrease individual toxicity. However, clinical experience and a review of experimental studies reveal that NSAIDs do not provide complete pain relief in all cases of canine osteoarthritis. In human medicine, a multimodal approach is frequently used for chronic pain associated with osteoarthritis.[32] A multimodal approach has also been suggested for the alleviation of chronic pain in veterinary species.[33]

The basis for suggesting a multimodal drug approach for the treatment of chronic pain stems from the recent understanding of the changes induced in the central nervous system as a result of the constant input of noxious signals from the periphery. Pain transmission involves a multiplicity of pathways, mechanisms, and transmitter systems. It is unlikely, therefore, that a single class of analgesic, whatever the dose, is going to provide complete analgesia. Clinical experience confirms this. The combination of two or more classes of analgesics (e.g., concurrent use of opioids, NSAIDs, and local anesthetics) is more effective for the control of perioperative pain.[34] A similar multimodal approach is recommended for the management of chronic pain, such as that associated with cancer or osteoarthritis.[33] The analgesic effect from these drugs is often supra-additive, or synergistic, and therefore, smaller doses of the individual drugs can be used, thus decreasing the likelihood of side effects from any one drug.

Nonsteroidal Antiinflammatory Drugs

NSAIDs form the basis of treatment of pain associated with osteoarthritis and other chronic pain. The fact that they are generally fairly effective in a variety of chronic pain conditions is due to their multiple mechanisms of action. In general, they interact with the cyclooxygenase enzymes (COX-1 or COX-2 or both), or cyclooxygenase and lipoxygenase (LOX) enzymes (dual inhibitors), inhibiting the production of many prostanoids (and leukotrienes [dual inhibitors]) involved in facilitating pain transmission. However, NSAIDs also act on other COX- or LOX-independent systems to help inhibit the transmission of pain. On a population basis, all NSAIDs are equally effective, but there is considerable individual variation. Thus we often see "individual responses" in terms of efficacy of NSAIDs.

The single most misleading claim or inference about the newer NSAIDs approved for use in dogs (carprofen, deracoxib, etodolac, firocoxib, meloxicam, tepoxalin) is that one NSAID is totally safe or much safer than others based on its pharmacology. The

adverse gastrointestinal tract effects of specific COX-2 inhibitors in general, and the coxibs in particular, have been extensively studied in humans.[35] This research has shown a marked reduction in gastrointestinal tract complications associated with these NSAIDs, compared with nonselective NSAIDs, in patients considered to be at low risk for such complications. In patients at high risk for gastrointestinal tract complications, however, the beneficial effect of coxibs and other selective COX-2 inhibitors are less clear. There is considerable current interest in the dual inhibitors in human medicine, again due to the thought that in a segment of the population they will provide significant improvements in GI tolerability, and also may affect the progression of osteosarthritis (both effects due to the inhibition of production of leukotrienes).[36] Very large epidemiological studies in humans have shown that renal toxicity is similar across all the NSAIDs, and also that cardiovascular toxicity is similar for all the NSAIDs. *Similar information from large-scale studies (thousands of patients) is not available in veterinary medicine*; however, smaller, well-controlled studies have shown that preoperative administration of injectable carprofen or meloxicam and preoperative adminstration of oral tepoxalin (dual inhibitor) had no adverse renal effects in normal dogs.[37-39] It is prudent, however, to assume that all the canine-approved NSAIDs can be associated with GI, renal, liver and cardiovascular side effects. GI problems are the most common side effects seen following NSAID administration to dogs.[40-43]

Therefore, preadministration screening and post-administration monitoring is very important. Screening and monitoring will identify most high-risk patients and help ensure successful use in the great majority of cases. Although not comprehensive, a suitable practical approach to screening is outlined in **Box 1**. Importantly, NSAIDs should be used at the manufacturers' recommended doses (**Table 4**) and not in close temporal association with other NSAIDs.[41]

If one NSAID does not produce the recommended efficacy or is associated with toxicity, the veterinarian can consider switching to another NSAID (see Figure 11). In the case of toxicity, this should be performed particularly cautiously. Based on current opinion leaders' recommendations, a minimum wash-out period of 5 to 7 days would be appropriate for an animal that has been treated with a non-aspirin NSAID or a shorter-duration corticosteroid (e.g., oral prednisone, dexamethasone), and switching is being performed due to poor efficacy in that individual. Particular care should be taken when considering animals given corticosteroids with an extended duration of effect, in which case a longer wash-out period is required (consistent with the duration of action of the extended-effect corticosteroid) is required. Aspirin deserves special consideration because of its profound effect on platelets. In cases of extended treatment with aspirin or doses exceeding 10 mg/kg, a wash-out period of at least 7 days is advisable. These guidelines may appear conservative, but until definitive information is published, the authors consider this approach to be appropriate.

When switching because of toxicity, the situation is less clear still. Appropriate treatment should be given, and sufficient time allowed for the adverse effects on tissue to resolve.

Adjunctive Drug Therapy

The decisions involved in delivering logical analgesic drug treatment to osteoarthritic patients are outlined in **Figure 11**. NSAIDs, paracetamol (acetaminophen), and steroids will often form the 'base analgesic' for the treatment of chronic pain. We are fortunate to have several NSAIDs that are approved for use in dogs with osteoarthritis, including COX-2 specific drugs and dual inhibitors, and the authors strongly recommend starting with an approved NSAID unless specifically contraindicated (see Table 4 for doses). If this proves to be ineffective, or poorly effective, one option is to change to another drug (with an appropriate wash-out period). Another option is to *add in other adjunctive drugs together with the administration of the 'base analgesic'* (see Figure 11) to attain acceptable levels of pain relief. Some of these adjunctive drugs are outlined here. These drugs are used with NSAIDs, and with non-drug therapies. Suggested doses of such drugs are given in Table 4. They can be used on their own, or in combinations, without NSAIDs if such drugs are contraindicated. Any drug treatment is only going to be optimized by:

- appropriate screening
- constant reevaluation of the patient (by veterinarian and, most importantly, the owner)
- constant vigilance for signs of toxicity.

Box 1. Practical Approach to Patient Screening Prior to NSAID Administration

NSAIDs have potentially lethal side effects. They should not be used in any animal that has not undergone adequate screening and post-treatment monitoring. Screening and monitoring is very important to identify high-risk patients and thus ensure successful use in the majority of cases. Adverse event reports related to NSAIDs may be disproportionately associated with older animals, so it is recommended that dogs 6 years and older be carefully evaluated for concurrent diseases and overall suitability. Although not comprehensive, a suitable practical approach to screening is outlined below. In some cases, following full consultation with the owner, a decision will be made to use NSAIDs despite the presence of a risk factor. In such cases, more frequent and targeted monitoring can be performed.

1. **Physical examination and patient's history:** A thorough physical examination, including the patient's history and identification of any previously administered medications, enables assessment of an animal's overall health and the possibility of drug interactions.
2. **Identification of preexisting diseases:** NSAIDs should be used with caution or not at all in animals with a history of NSAID-associated adverse reactions (although it is true just as there is a lot of individual variation in efficacy, adverse reactions are often very "individualistic"). Other NSAID contraindications include the following:
   - Evidence of gastric ulceration (e.g., melena) or GI disorders associated with mucosal damage. Risk factors for GI ulceration include:
     - History of GI ulceration: animals with a history of GI ulceration may be more prone to the GI toxic effects of any NSAID
     - Geriatric patients: older animals may have reduced drug clearance capacity and thus are at greater susceptibility to NSAID toxicity
     - Use of aspirin and inadequate wash-out period (i.e., <5–7 days) when switching between NSAIDs
     - Concurrent liver disease, renal insufficiency, mast cell neoplasia
   - Patients with renal insufficiency (documented by raised renal enzymes, and/or abnormal urine protein:creatinine ratios)
   - Patients with reduced hepatic function (most readily documented by raised liver enzymes and raised bile acids)
   - Conditions associated with low effective circulating volume (congestive heart failure, ascites, use of diuretics)
   - Pregnant animals
   - Cushingoid animals
3. **Hematologic and clinical chemistry evaluations:** It is important to determine hematologic and serum biochemistry baseline values before initiating treatment and periodically thereafter for any animal undergoing chronic therapy with NSAIDs (or any medication, for that matter). If clinical chemistry levels reveal renal or hepatic compromise, more frequent monitoring is essential if NSAIDs are used. There is no consensus on frequency of monitoring, but a baseline blood panel followed by a renal and liver panel 2 weeks after initiating treatment is advisable. Thereafter, monitoring clinical chemistry values every 6 to 12 months in young, healthy animals and every 2 to 3 months in older dogs is a reasonable approach.
4. **Determining and documenting concurrent drug use:** It is important to fully determine what other drugs an animal is receiving. Some medications may not have been prescribed by your veterinary practice. For example, many owners will use aspirin not realizing it is a NSAID, particularly if they themselves are on low dose aspirin and a NSAID. Concurrent use of NSAIDs with the following drugs is contraindicated or should be done with extreme caution:
   - Drugs that may be toxic to the kidney (e.g., the chemotherapeutic drug cisplatin)
   - Drugs that may be toxic to the liver
   - Drugs that modify renal PGs (diuretics, angiotensin-converting enzyme inhibitors, aminoglycosides)
   - Corticosteroids
   - Other NSAIDs, including any doses of aspirin.

(Adapted from Lascelles BD, McFarland JM, Swann H. Guidelines for safe and effective use of NSAIDs in dogs. *Veterinary Therapeutics* 2005;6:237-251.)

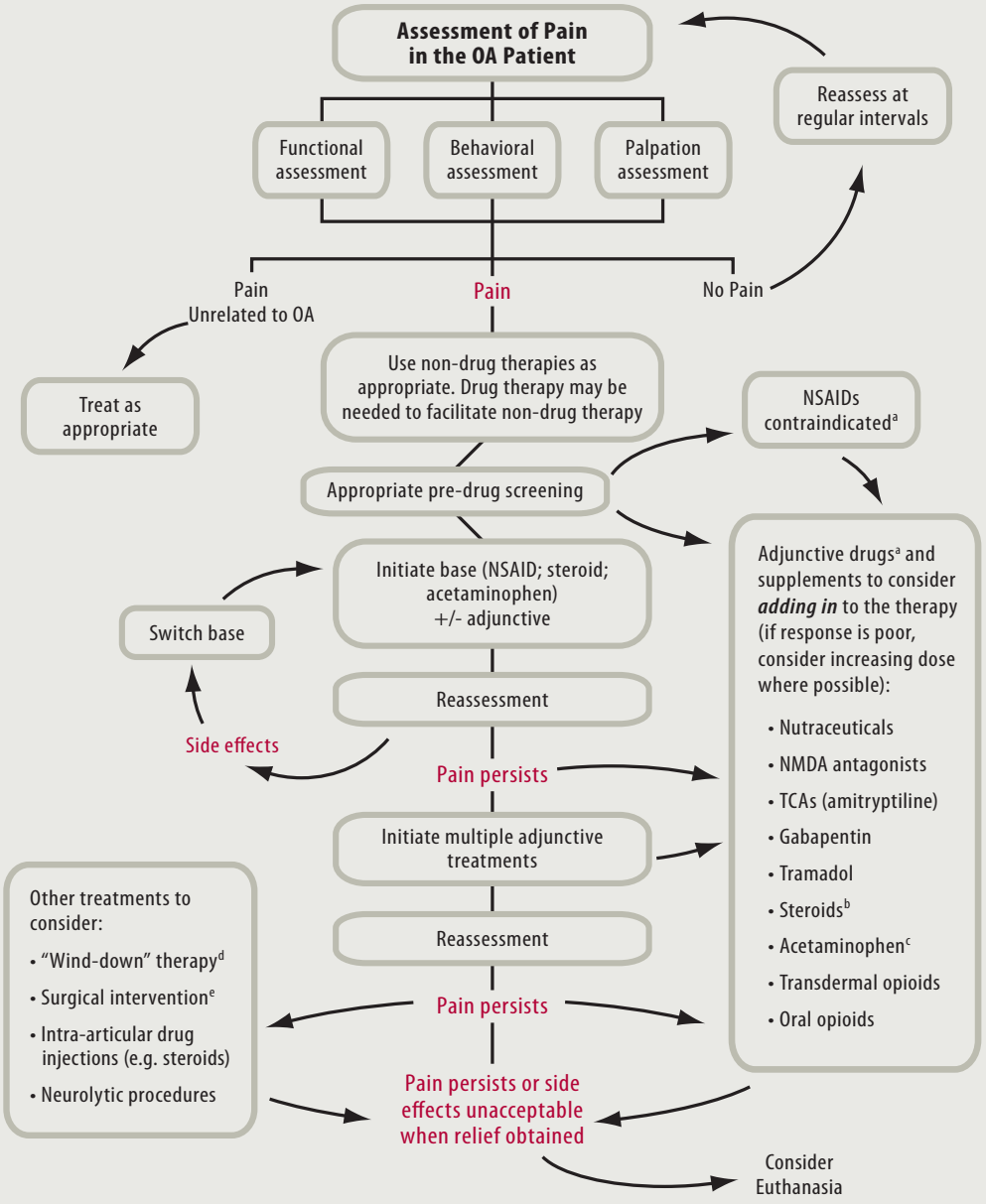
Table 4. Doses of NSAIDs Approved for Use in Dogs in the United States

Drug	Dosage Form	Indications	Dose	Precautions and Comments[a]
Carprofen (Rimadyl®, Pfizer Animal Health)	Caplets (25, 75, and 100 mg), chewable tablets (25, 75, and 100 mg), and injectable (50 mg/ml)	Approved for use in dogs to treat pain and inflammation associated with osteoarthritis and pain associated with soft-tissue or orthopedic surgery	4.4 mg/kg PO sid; 2.2 mg/kg PO bid; or 4.4 mg/kg SC	Safety not evaluated in dogs <6 weeks of age, dogs used for breeding, and pregnant or lactating bitches
Deracoxib (Deramaxx®, Novartis Animal Health)	Chewable tablets (25 and 100 mg)	Approved for use in dogs to control pain and inflammation associated with osteoarthritis and postoperative pain and inflammation associated with orthopedic surgery	Osteoarthritis: 1–2 mg/kg PO sid Postoperative: 3–4 mg/kg PO sid (7-day limit)	Safety not evaluated in dogs younger than 4 months of age, dogs used for breeding, and pregnant or lactating bitches
Etodolac (EtoGesic®, Fort Dodge Animal Health)	Tablets (150 and 300 mg)	Approved for use in dogs to treat pain and inflammation associated with osteoarthritis	10–15 mg/kg PO sid	Safety not evaluated in dogs <12 months of age, dogs used for breeding, and pregnant or lactating bitches
Firocoxib (Previcox®, Merial)	Chewable tablets (57 and 227 mg)	Approved for use in dogs to treat pain and inflammation associated with osteoarthritis	5 mg/kg PO sid	Safety not evaluated in dogs <10 weeks of age, dogs used for breeding, and pregnant or lactating bitches
Meloxicam (Metacam®, Boehringer Ingelheim Vetmedica)	Oral suspension (1.5 mg/ml) and injectable (5 mg/ml)	Approved for use in dogs to treat pain and inflammation associated with osteoarthritis	0.2 mg/kg PO on day 1, then 0.1 mg/kg PO sid; or 0.2 mg/kg IV or SC of injectable preparation on day 1 followed by 0.1 mg/kg PO sid	Loading dose can be administered SC or IV; not evaluated in dogs <6 months of age, dogs used for breeding, and pregnant or lactating bitches
Tepoxalin (Zubrin®, Schering-Plough Animal Health)	Zydis Rapidly-Disintegrating Tablets (50,100, 200 mg)	Approved for use in dogs to treat pain and inflammation associated with osteoarthritis	10 or 20 mg/kg on day 1, then 10 mg/kg	Not evaluated in dogs <6 months of age, dogs used for breeding, and pregnant or lactating bitches

[a]General precautions for NSAIDs: Do not use in patients with GI or renal disease; discontinue use if vomiting or diarrhea occurs; not recommended in hypovolemic or dehydrated patients or those with bleeding disorders; not for concurrent use with other NSAIDs or corticosteroids.

OPIOIDS. If pain relief with NSAID therapy is inadequate, oral opioid medications, such as codeine, codeine–combination drugs (such as acetaminophen-codeine), morphine, methadone, or butorphanol can be administered. Very little is known about the efficacy of oral opioids in dogs. Oral opioids are subject to a high 'first pass' effect in the liver, and recent work at the NCSU Pharmacology and Comparative Pain Research Laboratories suggests it is very difficult to provide any analgesia in dogs using oral morphine (immediate or extended release)[44] or oral methadone.[45] Transdermal fentanyl can also be used but is expensive for long-term use, and because of recent concerns about their safety in humans (http://www.fda.gov/medwatch/SAFETY/2005/safety05.htm#Fentanyl), may not be available in the future. The recent advent of buprenorphine patches in human medicine hold promise for providing longer term pain relief than with fentanyl patches. Side effects of opioids include sedation and gastrointestinal ileus, leading to constipation.

TRICYCLIC ANTIDEPRESSANTS. Tricyclic antidepressants (TCAs), such as amitryptyline and imipramine, block the reuptake of serotonin and norepinephrine in the central nervous system and so facilitate the body's own endogenous analgesic system. They also have antihistamine effects. These drugs have been used in humans for the treatment of chronic and neuropathic



[a] Adjunctive drugs and supplements may be used in combination without a NSAID, acetaminophen or steroid base, but are likely to be less effective.

[b] Steroids should not be used in combination with a NSAID.

[c] Acetaminophen has been used in combination with NSAIDs, but it probably increases the risk of GI ulceration.

[d] "Wind-down" therapy refers to the unproven technique of using combinations of intravenous analgesics over a 36 to 48 hour period in OA cases that are refractory to oral treatment in an attempt to "wind-down" the central nervous system changes and allow oral treatment to be more effective.

[e] Surgical intervention refers to total hip or other joint replacement and arthrodesis.

Figure 11.
Decision making in multimodal drug treatment of chronic pain associated with osteoarthritis.

pain at doses considerably lower than those used to treat depression. Amitryptiline has been used successfully for interstitial cystitis in cats,[46] a chronic pain syndrome. These drugs may have efficacy against osteoarthritis-induced chronic pain and chronic cancer pain in animals and other chronic pain syndromes in animals, but have not yet been systematically evaluated. The TCAs should probably not be used concurrently with drugs that modify the serotinergic system, such as tramadol.

ANTICONVULSANTS. Gabapentin is a structural analog of GABA (gamma-aminobutyric acid) and was originally introduced as an antiepileptic drug. While its analgesic mechanism of action is unclear, it appears to interact with NMDA receptors, possibly via effects on ion channels. The indications for gabapentin are unclear for veterinary patients, but it may be useful as an adjunct to other analgesics, especially for so-called neurogenic pain and pain from certain cancers such as bone tumors. Recent basic science studies in rats suggest it may have a role to play in the management of pain from osteoarthritis.[47]

NMDA ANTAGONISTS. Central sensitization is thought to contribute to injury or disease induced pain. The NMDA receptor appears to be central to the induction and maintenance of central sensitization,[48-50] and the use of NMDA receptor antagonists appears to offer benefit in the treatment of pain where central sensitization has become established, especially chronic pain. Amantadine is an NMDA receptor antagonist. Amantadine has been used for the treatment of neuropathic pain in humans, but as yet, has not been evaluated for the alleviation of pain associated with osteoarthritis One of the authors (BDXL) has been evaluating the NMDA antagonist amantadine (3-5 mg/kg orally once daily) as an adjunct to NSAID use and considers it to augment pain relief with a low incidence of side effects (mainly agitation and diarrhea). The dose of amantadine was decided upon on the basis of known kinetics,[51] clinical observations, and pilot data. Although we have not performed toxicity studies on amantadine, toxicity studies have been performed elsewhere.[51,52] In repeated dose toxicity studies conducted over a 2-year period, a dose of 40-80 mg/kg resulted in deaths after 30 weeks of administration; a dose of 40 mg/kg resulted in one death (out of 8 dogs) after 47 weeks of administration; a dose of 8 mg/kg was not associated with any adverse signs at all.

MIXED ANALGESICS. Although not classified as a true opioid, tramadol has weak binding affinity at mu-receptors and is thought to activate monoaminergic spinal inhibition of pain although this may not apply to non-primate species. It can be administered by multiple routes and is effective for chronic pain in humans and seems remarkably devoid of the usual undesirable side effects of opioids such as respiratory depression, nausea and constipation. Its kinetics have been studied in beagles.[53] One unpublished report in dogs is encouraging. Animals with chronic OA were treated with a low dose of ketoprofen (0.25 mg/kg PO daily) or low dose ketoprofen plus tramadol (5 mg/kg of prolonged release form PO daily) for 28 days. Dogs receiving both drugs had a greater improvement in pain scores, and even after treatment was discontinued they continued to improve while the dogs in the ketoprofen-only group remained static and had more incidences of acute flare ups after the end of treatment that the ketoprofen-tramadol animals.

CONCLUSION: MULTIMODAL DRUG AND NON-DRUG THERAPY

We have much to learn about both the efficacy and toxicity of various combinations of drugs, and non-drug therapy. Although much information can be successfully transferred from human medicine, veterinary patients are significantly different from humans both in terms of drug metabolism and efficacy, and in their musculoskeletal design. It is important that we obtain evidence based medicine on the management of veterinary patients, and that we keep in mind which recommendations are based on opinion, and which on scientific evidence. Suggestions given in this review may well change in the future as more information becomes available. In the light of little scientific information in this area, the successful use of multimodal drug and non-drug therapy for chronic pain can be greatly increased if veterinarians counsel clients on potential adverse effects and proactively ask for feedback on safety and efficacy, documenting this accurately. This will only occur successfully if the animal is reevaluated, and the owner interviewed regarding progress, on a regular basis.

THE FUTURE

The future of canine rehabilitation is very exciting as we start to see canine-orientated research define the optimal exercises and the optimal combinations of exercises at various stages of the rehabilitation program. Also, as more is understood about the specific neurobiology of canine osteoarthritis pain, so we will see the development of new drugs targeting the abnormalities present in the pain pathways in osteoarthritis.

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