

Treatment of Chronic Pain: Osteoarthritis

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Introduction

It has been estimated that osteoarthritis occurs in approximately 20% of the dogs seen in veterinary practice today and likely is that high or higher in cats. Pets are living longer with improved veterinary care while at the same time there is a growing incidence of obesity, contributing to acceleration of pain and lameness seen in animals with osteoarthritis as they age, gain fat and lose muscle mass. Chronic pain due to hip dysplasia, elbow dysplasia, cranial cruciate ligament insufficiency and late effects of osteochondrosis dissecans on the hock and shoulder mean the practitioner can see problems in almost every major joint in the dog on a daily basis.

In cats, Hardie and coworkers (2002) documented radiographic evidence of degenerative joint disease (excluding spine) in 64% of cats over 12 years of age in a retrospective study, with the elbow, hip, stifle and shoulders commonly affected. Radiographic evidence of hip dysplasia has been reported in up to 21% of Maine Coon cats, and in 6.6% (45/684) of cats of all breeds observed in a retrospective study (Keller 1999). Investigators have shown that approximately 25% of American cats studied (1,427) are overweight, and that heavy cats were 2.9 times as likely to be taken to veterinarians because of lameness not associated with cat bite abscesses than cats with optimal weight (Scarlett 1998). In this study, 4% of cats had lameness or joint disease.

Pathophysiology of Osteoarthritis

Although osteoarthritis is thought to be a non-inflammatory joint disease (as opposed to rheumatoid/immune-mediated arthritis or infectious arthritis), the truth is that there is an important inflammatory component, leading to synovitis, joint distension, stimulation of nerve fibers, and influx of inflammatory mediators in a vicious cycle. There can also be a large disparity between the severity of osteoarthritis even within one joint, for example in elbow dysplasia where the medial aspect of the joint may be completely denuded of cartilage while relatively healthy cartilage exists in the lateral compartment of the joint. Therapy should be aimed at reducing pain and inflammation, decreasing the load on damaged cartilage, and preserving the cartilage that is left. It is important to remember that, to date, osteoarthritis is neither curable nor reversible, although there is some promising work in cartilage resurfacing being done in humans.

Diagnosis

Prior to starting treatment for osteoarthritis, it is important that an accurate diagnosis be made and that criteria for response to treatment be established. Physical examination may yield clear evidence of osteoarthritis with palpable joint thickening and effusion, loss of range of motion, and palpable crepitus, however, radiographic confirmation is important to distinguish these signs from other

diseases that can mimic OA (rheumatoid arthritis, non-erosive arthritides such as chronic ehrlichiosis, neoplasia, pathologic fracture). In some instances, animals that appear to have limb lameness have neurologic or spinal disease (lumbosacral stenosis or instability, discospondylitis). It is not unusual to see animals in a referral practice that have been on NSAIDs for a long period of time but have no evidence of osteoarthritis seen on radiographs. Radiographs are the gold standard for establishing the presence or absence as well as the distribution of lesions. Radiographs can also provide a baseline for severity of osteoarthritis, however, in all species radiographic signs (mostly presence and size of osteophytes) correlate poorly to clinical signs. In cases where it is difficult to determine whether there is an intra-articular loose body that needs to be removed, computed tomography of the joint may be very helpful in making a decision between medical and surgical treatment.

Goals of Therapy

The clinician must decide “how will I know whether or not treatment is working in this particular animal?” prior to instituting a treatment and follow-up plan. Engaging the client is critical as they usually have a much better sense of how the animal is responding to treatment based on observation in the home environment. Use of a lameness questionnaire (dogs) or activity questionnaire (cats) can be very helpful in documenting changes over time (see Appendix I). Lameness diaries documenting specifics such as distance the pet is able to walk comfortably, when lameness is worse or better and so on can also be very helpful. Some clients are also happy to video their animals, which can be particularly helpful when treating a subtle lameness or a performance animal. Assuming that force plate analysis is not available, additional indicators such as measurement of limb circumference over time (as an indicator of increasing or decreasing muscle mass), goniometry and weight loss can be objectively measured and recorded.

Treatment:

Weight loss is the most valuable tool the clinician has in the treatment of osteoarthritis in the overweight patient. The overweight animal is caught up in a vicious cycle of weight gain due to inability to exercise, with resultant worsening of pain and disability. Many of these pets are presented for a change in personality, while some owners confuse depression associated with inactivity and chronic pain as a normal aging change. Looking for and treating possible underlying causes for weight gain, particularly hypothyroidism and Cushing’s disease in dogs, can remove obstacles previously preventing weight loss despite seemingly appropriate dietary restrictions. The use of weight reduction programs (there is a good one at <http://www.vet-medicine.net>: go to weight reduction calculator; no username or password is required) is very helpful.

We all familiar with the road blocks that occur that can prevent success of weight loss plans, such as shared feeding between multiple animals in the household, excessive snacks, diet sabotage by certain members of the family, and the client’s perception that their animal is not overweight or that the diet

recommended is cruel because the animal may be hungry. However, for every client that is likely to be noncompliant, there are 2 that will comply if given a good plan with appropriate positive reinforcement and follow-up. There are as many ways as vets to approach this problem of compliance. Things that may help include:

- Easy access to a scale where clients may drop in and weigh their pets without disturbing the clinic routine or tying up a technician or doctor's time
- Having a technician with experience in helping animals to lose weight counsel the client and contact the client for follow-up on a scheduled basis
- When cutting food intake by 1/3, substitute twice the volume of the "missing" food with canned pumpkin to avoid excessive hunger
- Recommend low-calorie treats, such as green beans and broccoli (these can also be mixed into canned dog food)
- Providing a weight loss handout using a computer program that gives the client a fairly accurate idea of how long it will take for weight loss to occur.
- Change the diet to a "joint diet" such as Purina J/M or Hill's J/D while controlling caloric intake at the same time
- Documenting previous weight gain and how it has contributed to the animal's current problems (clinic records often show an insidious weight gain over time that is easy to access)

Exercise. Many clients are under the impression that they will do more damage to arthritic joints with exercise and that their pet will no longer be able to perform activities as it once was. Although very high-impact activities (agility work) may be out of reach, the benefits of low-impact exercise, such as walking and swimming, far outweigh any theoretical concerns about cartilage damage. A modest increase in muscle mass can allow an animal to protect a damaged joint, while exercise can also improve the animal's mood and help treat depression associated with chronic pain. Very simple activities, such as a quarter mile walk once to twice daily, can lead to significant weight loss over time. Clients whose lifestyles are not conducive to dog walking may be able to find alternatives in the form of a neighbor, pet-sitting service or "doggy daycare" service that can exercise their dogs on a daily basis.

Drugs: NSAIDs

Non-steroidal anti-inflammatory drugs are utilized heavily for the treatment of osteoarthritis for the simple reason that they are very effective in decreasing pain and inflammation, by inhibition of the cyclooxygenase enzyme. NSAIDs commonly used by veterinarians have included *aspirin, *phenylbutazone (which is licensed for use in the dog), *flunixin meglumine, *ketoprofen, *piroxicam and naproxen. Side effects have been the limiting factor in their clinical use, most often GI but also renal and platelet inhibition. Although side effects are common, there is a great deal of individual variation in response to these traditional

NSAIDs, and some dogs can tolerate these drugs long-term for the treatment of OA, however, those dogs are usually the exception rather than the rule.

Selective vs non-selective NSAIDs. The development of a newer class of NSAIDs that is more specific in inhibiting only COX-2, thought to be the inducible or inflammatory form of COX while sparing COX-1, the “housekeeping” or “good” COX has led to products that have a much improved gastrointestinal safety profile. Examples of drugs in this class include *deracoxib (COX-2 specific) and *meloxicam (COX-2 preferential). Drugs such as *carprofen or *etodolac are not as COX-2 specific as deracoxib, but still have a much improved GI safety profile over aspirin or phenylbutazone. Important things to remember about “COX-2” or “COX-1 sparing” NSAIDs are that they have the same renal effects as the older nonselective NSAIDs, they still can cause GI side effects in a certain percentage of animals, including GI perforation and they can have unexpected side effects, as recently seen with the human products Vioxx (rofecoxib) and Celebrex, linked with cardiovascular side effects (myocardial infarction) when used at high doses for the treatment of chronic pain. As it turns out, some COX-2 is actually physiologic for certain body systems and COX-1 may also be formed in response to some inflammatory processes. In the case of the newer coxibs, these agents suppress the formation of prostaglandin I₂, the mediator produced by endothelium that induces vasodilation, inhibits platelet aggregation, and prevents the proliferation of vascular smooth muscle. Unlike aspirin and nonselective NSAIDs, COX-2 inhibitors do not stop platelets from making thromboxane A₂, the COX-1 product that constricts blood vessels, aggregates platelets, and causes vascular proliferation.

The clinician should also note that any NSAID can cause gastrointestinal perforation with minimal to no clinical signs leading up to the event, and that prophylaxis with gastric protectants (sucralfate), H₂ blockers, proton pump inhibitors or misoprostil, while effective in the treatment of ulcers once they are present, will not prevent ulceration from occurring.

***Tepoxalin (Zubrin)** has recently been approved for treatment of osteoarthritis in the dog and is a non-selective NSAID that also inhibits the 5-lipoxygenase pathway which forms inflammatory leukotrienes. Tepoxalin is referred to as a dual acting anti-inflammatory drug. It is unclear as yet what clinical advantages this offers in the treatment of chronic pain associated with osteoarthritis, however theoretically decreasing leukotrienes may decrease inflammation associated with OA.

***Acetaminophen** is a non-acid NSAID that may work with a completely different variant of the COX enzyme known as COX-3, present in CNS tissues. Although highly toxic in the cat, it can be used in dogs with or without codeine and may be especially useful in dogs that have renal compromise or are especially sensitive to GI side effects of other NSAIDs.

Corticosteroids

Corticosteroids (CCS) effectively manage the pain and inflammation associated with tissue damage by blocking the inflammatory cascade at an even

higher point than NSAIDs do, CCS block the conversion of phospholipids into arachadonic acid by inhibiting phospholipase A2. It is a frequent observation that animals on CCS for other reasons (skin, immune mediated disease) have concurrent improvement in chronic lameness, while Cushing's patients often experience worsening clinical signs associated with osteoarthritis as their excessive endogenous CCS return to normal levels. Because chronic CCS are associated with a high incidence of side effects, they are not used for treatment of chronic OA, however, intra-articular CCS are frequently used successfully in humans. In dogs, intra-articular CCS use is often recommended for biceps tenosynovitis early in the course of disease and can be very effective. The clinician should be cautious, particularly in advanced OA of the risk of joint infection and warn the client of that risk. In addition, it is recommended that limited and low-impact exercise be prescribed for the first few weeks after injection as the cartilage may be excessively soft. The clinician may want to consider intra-articular injection with hyaluronic acid (HA) before resorting to IA CCS.

Disease-Modifying Osteoarthritis Agents (Chondroprotectives).

Agents, whether they are drugs or dietary supplements, that are specifically aimed at treatment of the cartilage itself, primarily to prevent further degeneration of the already compromised cartilage, are termed disease-modifying osteoarthritis agents. In theory, these products claim to enhance chondrocyte or synoviocyte metabolism and in some cases reduce inflammatory mediators.

Polysulfated glycosaminoglycan (Adequan®, PSGAG)

PSGAG is an injectable drug with good evidence of efficacy in both cell culture and research animal models, and has undergone FDA approval. Polysulfated glycosaminoglycan is a semi-synthetic glycosaminoglycan prepared by extracting glycosaminoglycans (GAGs) from bovine tracheal cartilage. PSGAG is approved for both the dog and horse. It is also used off-label, at half the canine dose, in the cat with anecdotal success. Adequan has both anti-inflammatory properties and an anabolic effect on collagen, proteoglycan and hyaluronic acid synthesis. The manufacture lable suggests dosing at 4 mg/kg, IM, twice weekly up to 8 treatments, and thereafter as needed.

Chondroitin sulfate and glucosamine are orally administered, over the counter nutritional supplements or dietary additives. While there is some evidence in people supporting their use, this remains controversial (see this month's JAVMA!). The theory behind the use of these agents is that they provide needed precursors that will enable diseased chondrocytes to form normal hyaline cartilage in an efficient manner, hopefully tipping the scales away from continued cartilage degradation back towards production of healthy cartilage. There is no regulation of the amount of quality of CS or glucosamine in the many commercial products that are available, therefore what's on the label and actually in the bag may not match.

Hyaluronic Acid (HA). Hyaluronic acid and sodium hyaluronate are nonsulfated glycosaminoglycans and have been shown to be superior to placebo or arthroscopic lavage for control of pain and clinical signs associated with knee arthritis in humans. Anecdotally, they work well in dogs given IA every 3-12 months. The animal is lightly sedated, the joint aseptically prepared, joint fluid aspirated and reserved for diagnostics (particularly if there is ANY chance of infection) and 1-3 mls of sodium hyaluronate injected.

Narcotics

Oral preparations of narcotics suitable for dispensing and home use by owners have become more available in the past few years. However, much work is yet to be done on bioavailability and efficacy in dogs and cats, particularly for chronic pain. Oral **butorphanol**, which was initially thought to be a useful analgesic in dogs, has a very short half-life and is probably not appropriate for use in treatment of chronic pain. Oral sustained release morphine has recently become popular, particularly in combination with a NSAID or as a washout drug when switching from one NSAID to another (particularly a non-selective to a selective). A recent abstract from ACVIM 2004 suggests that **oral sustained release morphine** is poorly orally available and serum levels were inconsistently, discouraging us from using it although for almost a year we were using it frequently for post-operative pain.

The injectable preparation of ***buprenorphine**, given buccally or sublingually, has become very popular for post-operative pain in the cat and may be useful for treating breakthrough pain in cats with OA in combination with meloxicam or by itself in cats that cannot tolerate NSAID therapy. Although it may also be given orally in dog, to our knowledge this is not commonly performed.

Tramadol* (Ultram®: Ultracet® includes acetaminophen!) is a synthetic mu-receptor opiate agonist that also inhibits reuptake of serotonin and norepinephrine, all of which contribute to its analgesic properties. It is not controlled although that may change as there is potential for human abuse. There is quite a bit of anecdotal use in the dog (including at TAMU), and some in the cat although we prefer to use buprenorphine buccally in the cat. There is very little information as to clinical efficacy in dogs and pharmacokinetics in the cat to date. We often use it in combination with a NSAID or for washout between NSAIDs in dogs with OA.

NMDA receptor antagonists

Chronic pain involves different pathways than acute pain. In chronic pain, a phenomenon known as “wind-up” occurs, involving an increased recruitment and lower threshold of depolarization of the C fibers, the slow pain fibers responsible for transmitting information about noxious stimuli from peripheral to the CNS. Chronic pain involves the upregulation of the NMDA receptor (found on

the receiving end of the dorsal horn neuron), which is key in the perpetuation of allodynia, which is sensation of pain resulting from a normally non-noxious stimulus, and hyperalgesia, which is an exaggerated response to painful stimuli. It is thought that until this NMDA receptor is “switched off” that conventional pain therapy may be ineffective in patients with chronic pain. Examples of NMDA receptor antagonists include ketamine, gabapentin and amantadine. Generally they work best in conjunction with other drugs in a multi-modal approach, rather than by themselves.

***Gabapentin** is an anticonvulsant that can also have analgesic effects via its NMDA receptor antagonist function, although neither of these effects is well-understood. There is very limited experience in veterinary medicine with its long-term use, and it should be used with caution in patients with diminished renal function. Sedation is the most likely side effect, however, the adverse profile effect is not well-established in animals. Gabapentin may also be a useful drug in the treatment of chronic neuropathic pain (ie, chronic intervertebral disk disease).

***Amantadine** is an antiviral drug that also has NMDA receptor antagonist properties, there is very limited experience with its use in animals for treatment of chronic pain. As opposed to gabapentin, dogs may exhibit agitation and GI side effects, especially early in therapy and overdoses can be potentially very serious. In humans it is also used as an antiparkinsonian drug.

Alternative Drugs

***Amitriptyline** is a tricyclic antidepressant that is primarily used for behaviour disorders and neuropathic pain in small animals, and its use has recently been suggested as an addition to other drugs for the treatment of chronic OA. It has a complex pharmacological profile and alters neurotransmitters via at least 3 different mechanisms. It may reduce the seizure threshold in epileptic animals, is associated with sedation and anticholinergic effects but overdoses can be very toxic in both animals and humans.

***Doxycycline** can be useful in animals with chronic joint pain in 2 ways: one it is the most effective treatment for chronic, joint associated ehrlichiosis, which does occur with some frequency in our area and can be very difficult to diagnose and secondly it is also a matrix-metalloprotease inhibitor, which means that it can actually decrease inflammation in the osteoarthritic joint.

***SAMe**. S-Adenosyl-Methionine is a nutraceutical that is most commonly used as an adjunctive treatment for liver disease but also may be useful in the treatment of chronic OA and the depression that can go along with it. It is very safe and there are apparently no contraindications to its use, other than possible interactions with drugs such as tramadol or other antidepressants which could cause additive serotonergic effects.

***Fatty acid supplements**. Fatty acids/essential/omega/fish oil dietary supplements are usually used in the form of commercially available veterinary products containing fish oil (eicosapentaenoic and docosahexanoic acids), vegetable oil (gamma linolenic acid) that serve as essential fatty acids. The particular therapeutic benefits and ratios of omega-3 vs omega-6 FA in the treatment of chronic OA are still being debated. Side effects may include

prolonged bleeding times, so be cautious if using in combination with PSGAG or aspirin therapy.

Physical Medicine

Physical medicine is a rapidly growing area of veterinary medicine, with at least 2 certification programs available in **rehabilitation** medicine (the term physical therapy is limited to treatment of humans by a physical therapist ONLY), and others available in acupuncture, massage and chiropractic. While the evidence basis for much of this is yet to be done, physical therapy is well-documented to be effective for certain disease states in humans and much of what we do in veterinary medicine can be helpful for the chronic OA patient.

In our practice, water treadmill therapy is helpful in a) unloading the joints and allowing the patient to use the limbs and build up some muscle without overstress (particularly in obese dogs). Massage, heat and active range of motion exercises all can play a part in a multimodal attack in the aggressive treatment of osteoarthritis in both dogs and cats.

Acupuncture is also used in our practice for the treatment of chronic OA. The Western principle that is most often used to explain how it may work is the theory that acupuncture stimulates endogenous opioid production, alters pain neurotransmitter release, stimulates inhibitory neurons in the CNS that block or “gate” pain transmission and alters blood flow. Some good evidence based medicine is beginning to appear in the human literature (Berman 2004).

Summary:

A multi-modal approach, tailored to the animal and the client, is the best way to achieve success and can provide years of good quality life for animals with osteoarthritis. Weight loss may be the single most effective tool that the veterinarian has to improve clinical signs, however, judicious use of other modalities, including drugs, nutraceuticals and rehabilitation may give the animal the break from the vicious cycle of pain long enough to get up, go out and exercise the weight off. As we continue to see new drugs and new modalities arrive and have old ones disproved (see oral morphine!) it is important that clinicians constantly stay informed in order to most effectively treat the most common chronic pain syndrome seen in veterinary practice today.

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APPENDIX 1
Feline Activity Assessment

Case Number _____

Owner's Name _____

Clinician _____

Cat's Name _____

Referring Veterinarian _____

Evaluator _____

Please **Read Instructions First:**

- Reply to the questions by **placing a vertical mark** on the corresponding line. This vertical mark corresponds to a place between the two extremes. The distance between your mark and the left end will be measured to quantify your response.
- Please **notice the labeling** on the left and right sides before marking it.
- When assessing your cat over the past week (or month), mark down his/her **usual condition**.
- **Thank you!**

1. How would you describe your overall assessment of your cat in the last month?

|-----|
poorexcellent

2. How has your cat's attitude been in the last month?

|-----|
negativepositive

3. How frequently does your cat display comfort or "happy cat" postures (for example, lying on back in a relaxed position)? Not applicable:

|-----|
rarelyfrequently

4. What type of daily activities does your cat engage in (ie., jumping on and off furniture, playing with toys or other pets)?

Less grooming

More

Thank you for completing this questionnaire.