PEER REVIEWED

MANAGING CHRONIC PAIN IN DOGS & CATS

Part 1: The Two Most Important Tools in the Treatment of Osteoarthritis

Mark E. Epstein, DVM, Diplomate ABVP (Canine/Feline), CVPP

In many ways, discussing treatment of chronic pain defies the limitations of a review article. In human medicine, entire textbooks are devoted to the topic; in fact, entire textbooks are devoted to *different types* of chronic pain.

Chronic pain is not a singular disease—it takes on many different forms and occurs for many different reasons, with a variety of individual expressions. However, there are commonalities and basic principles that lend guidance in development of treatment plans:

Principle #1. There is no functional purpose to chronic pain; there is no evolutionary advantage to it, and it serves no helpful end.

Principle #2. Chronic pain almost always involves a degree of sensitization, both *centrally* in the dorsal horn of the spinal cord and *peripherally* at the pain-generating site. This sensitization (**Table 1**), also termed *wind-up*, amplifies perceived pain (and its impact) beyond what the underlying pathology would otherwise produce (and, sometimes, even in its absence).

Principle #3. Given the nonverbal and adaptive behaviors of dogs and cats, it is difficult for owners to perceive their pets' chronic pain; what they *can* see are mobility issues that can be described as progressive *disability*.

Principle #4. Chronic pain in humans, controlling for other factors, is considered comorbid with diminished cognition (learning, memory, mental acuity) and clinical depression; while we have no data with regard to dogs and cats, it is hard to imagine that some elements of this pathophysiology do not exist in nonhuman animal species.

Principle #5. Under-recognized and under-managed chronic pain can result in death via humane euthanasia, perhaps years earlier than would otherwise be necessary. Thus, one can believe that the recognition and management of chronic pain—in whatever form—is equally as life-preserving as any actions taken to handle acute and critical conditions in veterinary patients.

Veterinarians encounter chronic pain in the following domains:

- Osteoarthritis (OA)
- Chronic or chronic–active inflammatory pain not related to OA
- Maladaptive chronic pain not related to OA or cancer[1]
- Cancer pain, especially osteosarcoma or other bone metastasis.

This series is split into 3 articles:

1. Part 1 will discuss the two most important strategies for management of pain associated with OA
2. Part 2 will discuss additional modalities for management of pain associated with OA
3. Part 3 will discuss management of causes of chronic pain not related to OA.

OVERVIEW OF OSTEOARTHRITIS

OA, statistically the most common chronic pain condition in dogs and cats, is challenging to treat due to the difficult nature of early recognition and its inevitably progressive pathology. Note that the veterinary literature generally describes the condition as OA in dogs and degenerative joint disease (DJD) in cats. While their pathophysiology may be dissimilar, this article will use the term OA for both species.

Origin of Pain

OA is typically thought of as a disease of bone and cartilage, and physical examination often easily elicits signs attributable to osteophytes and crepitation. However, the pain of OA is not felt at the articular surfaces or what is left of them; rather, pain is largely felt in the peri-articular structures, such as pain due to inflamed synovium; tension placed on a fibrotic joint capsule; and patients exerting pressure on weakened ligaments, tendons, and muscle. Thus, OA is a disease of the entire joint, including synovitis, fibrosis, and atrophy, and it results in pain *and* progressive disability.

Neuropathic Component

In recent years, OA has been affirmed to include a neuropathic component (in 25% of humans with knee OA[2] and, in 1 pending study, 25% of cats with hip OA[3]). It is most likely safe to surmise that OA universally involves a *maladaptive*—even

TABLE 1. HYPERSENSITIZATION: TYPES & PATHOPHYSIOLOGY

PERIPHERAL SENSITIZATION
• Increased receptor expression at nerve endings
• Lowered firing thresholds of nociceptors
• Antidromic signaling from the dorsal horn to the periphery
• Neurogenic inflammation and recruitment of "innocent bystander" nerve fibers
• Expansion of the nociceptive field
CENTRAL SENSITIZATION
• Activation of N-methyl-D-aspartate (NMDA) and other receptors
• Sustained opening of ion channels and depolarization of second-order neurons
• Involvement of potent excitatory amino acids, such as substance P
• Hypopolarization of second-order neurons
• Activation of glial (local immune) cells
• Sprouting of nerve endings and resultant cross-talk with neurons from other geographic areas of the body and those that normally serve other purposes (touch, pressure, mechanoreceptors)
• Neuron gene-expression and phenotypic changes

if not abjectly neuropathic—pain state in most patients. Maladaptive pain is "pain as disease"—disproportionate to the extent of the underlying pathology.

Conformation Component

Much, if not most, canine OA is not merely wear-and-tear in origin but conformational (**Table 2**). Cats, both young and old, appear to have a very high incidence of OA, with up to 60% to 90% of cats across all ages exhibiting radiographic changes consistent with OA.[4]

Although the pathophysiology of OA may be different in dogs and cats, OA in both species begins early in life—far earlier than in humans. Our therapeutic efforts to address OA in patients, therefore, may be quite different from one life stage to another.

MANAGEMENT OF OSTEOARTHRITIS

Despite the complexities discussed, it is possible to devise evidence-based OA management plans. Fortunately, systematic reviews of treatment of OA and nonsurgical management of hip dysplasia in dogs[5,6] and very good review articles about OA in cats are available.[7]

The 2 modalities at the top of the evidence-based pyramid for management of OA are:

- Weight optimization
- Nonsteroidal anti-inflammatory drug (NSAID) therapy.

Weight Optimization

Weight optimization is a chief strategy for management of OA. Adipose tissue is a major endocrine organ, and most of the substances that it secretes into the circulation are pro-inflammatory cytokines, which infiltrate the synovium of the joint and dorsal root ganglia and contribute to OA pathology and neurologic sensitization.

Scientific Studies

Evidence is strong that a healthy body weight is likely the most effective preventive tool against the development and progression of OA in dogs, even (or perhaps especially) in predisposed breeds.[8,9]

- In one sentinel study, Labradors maintained at a lean body composition had a lifespan nearly 2 years longer than those allowed to free-feed and become overweight, with OA-related mobility issues being the dominant cause of euthanasia in overweight/obese dogs.[10]
- In overweight dogs with existing hip dysplasia or OA, multiple studies and systematic reviews demonstrate clinical improvement in patients that underwent weight loss,[5,11] with one demonstrating improvement following only a 6% reduction in body weight.[12]

In cats, obesity led to a 4 times higher risk of presentation to a veterinarian for clinically relevant lameness[13]; although, other feline studies have found only a weak correlation between body condition score (BCS) and radiographic OA changes.[14]

Dual Purpose

The benefit of weight optimization, from both a preventive and treatment perspective, is quite clear. Indeed, a high BCS most likely dramatically, and negatively, affects a dog's propensity for OA and severity of disease. In an overweight patient, weight loss should be a primary treatment rather than a secondary afterthought.

NSAID Therapy

Unfortunately, many dogs and cats with existing OA cannot exercise to lose weight due to the underlying pain and inflammation caused by the disease. Furthermore, at its core, OA is an inflammatory disease that leads to central and peripheral sensitization. Therefore, NSAIDs are a key pharmacologic intervention for OA in both dogs and cats (**Table 3**, page 22).

Several excellent systematic review articles provide detailed guidance for the best use of long-term NSAIDs in both dogs[15-17] and cats.[18,19] A comprehensive discussion of

TABLE 2. Canine Conformational Origins of Osteoarthritis

- Chondrodysplasia
- Elbow dysplasia (coronoid, anconeal)
- Heritable predisposition to cruciate ligament disease
- Hip dysplasia
- Luxating patella
- Osteochondritis dissecans

Table 3. Chronic Pain Management: Veterinary NSAIDs Approved for Treatment in the U.S.

DRUG	DOSAGE
Dogs	
Carprofen (Rimadyl, zoetisus.com; Novox, vedco.com)	4.4 mg/kg Q 24 H or 2.2 mg/kg Q 12 H
Deracoxib (Deramaxx, us.novartis.com)	1–2 mg/kg Q 24 H
Firocoxib (Previcox, merial.com)	5 mg/kg Q 24 H
Meloxicam (OroCAM, abbott.com)	0.1 mg/kg Q 24 H
Cats	
In the U.S., meloxicam (injectable solution) and robenacoxib (Onsior, usnorvartis.com) are only approved for postoperative pain in cats. See **Management of Chronic Pain in Cats** (November/December 2012, available at **tvpjournal.com**) for guidelines on use of these drugs in cats.	

NSAIDs is beyond the scope of this article, but basic conclusions include:

Long-Term Use & Safety

- Regular use of veterinary-approved NSAIDs at label doses for canine OA can lead to continued improvement over 6 months[20] to 1 year.[21]
- Cats metabolize meloxicam and robenacoxib by oxidation, not glucuronidation.
  - » Several studies demonstrate safety of long-term oral meloxicam at below-label doses (off label in the U.S. but approved in the EU),[22] including one study in cats with chronic renal disease whose creatinine values slightly improved during the study period.[23]
  - » Robenacoxib has demonstrated safety in cats at 5 times and 10 times the labeled dose for 6 months[24] and 6 weeks,[25] respectively.
- Approximately 95% to 97% of dogs can receive veterinary-approved NSAIDs at labeled doses and frequency up to 3 months or longer without adverse events.
- No veterinary-approved NSAID has been shown to be safer, or less safe, than any other.
- Veterinary-approved NSAIDs are safer than non-approved veterinary NSAIDs.

Adverse Effects

- The most common adverse events are gastrointestinal (GI) in nature; clinical signs noted are (in order of most common): vomiting, diarrhea, and inappetance for dogs, and inappetance in cats.
  - » Adverse effects most often occur within 2 to 4 weeks of initiating treatment, and clinical signs usually resolve when the drug is withdrawn and gastroprotectant therapy is initiated.
  - » Gastric erosion and ulcers can occur during NSAID therapy, and it is possible, but unlikely, for these conditions to manifest without clinical signs and lead to perforation.
- The most common reason for perforation is concurrent use of another NSAID or corticosteroid, administration of high dosages, or a combination of these.[26]
- The second most common adverse effect is nephrotoxicity; patients at highest risk are those with low-flow states (ie, hypotension, hypovolemia, congestive heart failure, sodium depletion, furosemide administration) and/or pre-existing chronic renal disease.
- Idiosyncratic hepatocellular necrosis remains exceedingly rare (0.015%) and it is not a toxicosis, but an intrinsic, heritable reaction to the molecule being administered.[17]
- Adverse effects of NSAIDs can be minimized by the simple act of appropriate use.

IN SUMMARY

Many other tools are available for OA management in dogs and cats, but weight optimization and NSAID therapy are supported by the very highest levels of evidence and other modalities are considered adjunct to these 2 main therapeutic measures.

There is, however, a role for other pharmacologic and nonpharmacologic modalities to manage the chronic maladaptive pain of canine and feline OA, and these modalities will be discussed in Part 2 of this series. ■

BCS = body condition score; DJD = degenerative joint disease; GI = gastrointestinal; NMDA = N-methyl-D-aspartate; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis

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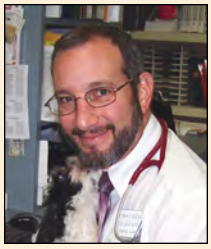

***Mark Epstein**, DVM, Diplomate ABVP (Canine/Feline), CVPP, received his DVM from the University of Georgia and is the senior partner and medical director of TotalBond Veterinary Hospitals as well as Carolinas Animal Pain Management, a group of AAHA-accredited practices in the Charlotte and Gastonia, North Carolina, areas. He is certified by the American Academy of Pain Management and International Veterinary Academy of Pain Management, and a past president of the IVAPM and ABVP. Dr. Epstein is an author and frequent lecturer on the recognition, prevention, and treatment of pain in the veterinary clinical setting.*

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