

MANAGING CHRONIC PAIN IN DOGS & CATS

Part 2: The Best of the Rest in the Management of Osteoarthritis

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Part 1—**The Two Most Important Tools in the Management of Osteoarthritis** (November/December 2013, available at tvjournal.com)—of this 3-part series addressed basic principles of chronic pain and also discussed treatment for its most common manifestation in companion animals: osteoarthritis (OA).

While Part 1 dealt with the 2 most important considerations in OA therapy: weight optimization and non-steroidal anti-inflammatory drug (NSAID) therapy, this article discusses other modalities—both pharmacologic and nonpharmacologic—for treatment of canine and feline OA.

TOP 3 MODALITIES

Well-designed, systematic reviews evaluating treatment of OA and nonsurgical management of hip dysplasia in dogs are now available.^{1,2} Very good review articles are also available for cats diagnosed with OA.³

Based on these evidence-based perspectives—once weight optimization and NSAID therapy have been implemented—3 modalities rise to the top of the list.

1. Polysulfated Glycosaminoglycans

Veterinary polysulfated glycosaminoglycans (PSGAGs) administered by the **parenteral route** (ie, IM injection) have met both regulatory scrutiny and quality control measures; independent studies appear to support their clinical utility.^{4,5} Examples include (Table 1):

- PSGAG (Adequan Canine, novartis.com)
- Sodium pentosan polysulfate (Cartrophen Vet for Dogs, biopharmaus.com.au).

In contrast, clinical evidence for **oral nutraceuticals**

is limited in dogs and cats and, at best, conflicting in humans. However, it can be argued that initiating use of oral nutraceuticals early in life, particularly for at-risk breeds, is safe and may provide some long-term chondroprotective effect.

If nutraceuticals and oral supplements are used, caution is warranted due to the following concerns:

- Degree of quality control
- Potential drug interactions, especially with NSAIDs, because some over-the-counter products contain aspirin or other cyclooxygenase (COX)-inhibiting agents
- Ingredients derived from endangered species
- Need for clinical studies to demonstrate efficacy.

2. Omega-3 Fatty Acids

Several randomized placebo-controlled blinded studies⁶⁻¹⁰ and one systematic review¹¹ have demonstrated the efficacy of diets rich in:^{12,13}

- Eicosapentaenoic acid (EPA) for dogs with OA
- Docosahexaenoic acid (DHA) for cats with OA.

The availability of multiple randomized placebo-controlled blinded studies and systematic reviews place these data high on the evidence-based pyramid. However, this type of supplementation should be reserved for pets at a healthy weight.

TABLE 1. On- and Off-Label Use of Polysulfated Glycosaminoglycans

	On-Label Dose: Dogs	Off-Label Use	Comments
Adequan	4.4 mg/kg IM twice weekly for 4 weeks	<ul style="list-style-type: none"> • Dogs and cats • Administer SC • Continue on long-term basis, (eg, Q 1 month and adjust frequency according to patient needs) 	Caution with patients at risk for bleeding dyscrasia
Cartrophen Vet	3 mg/kg SC Q 5–7 days, 4 times	<ul style="list-style-type: none"> • Continue on long-term basis, (eg, repeat protocol Q 4–6 months) 	

Gate Theory of Pain

The spinal cord has a functional, neurophysiologic “gate” that can either block or allow pain signaling to the brain;¹⁶ by sending other signals to the brain during exercise (eg, proprioception), pain signaling through the spinal cord “gate” is, to a degree, blocked.

3. Therapeutic Exercise

While a relatively new modality in veterinary medicine, controlled, prescribed exercise is well established in humans for amelioration of pain related to OA. There is every reason to believe that dogs and cats can benefit as well due to a variety of mechanisms, including:

- The Gate Theory of pain
- Activation of endogenous opioids
- Enhanced strength of periarticular soft tissue (eg, muscle, tendon, ligament) and resulting improved microstability of joints
- Weight loss (if needed).

Some studies already support use of this modality in painful dogs with OA.^{14,15}

ADDITIONAL OPTIONS

The evidence for other recommended treatments for OA pain is either limited, weak, conflicting, or based on *in vitro* cellular/molecular rather than clinical data. However, modalities that may play a role in management of OA in dogs and cats include:

- Pharmacologic (pain modifying analgesic drugs)
- Nonpharmacologic
- Biologic.

Pharmacologic Therapy Options (Table 2, page 29) *Gabapentin*

No clinical studies evaluating gabapentin—as a single agent or an adjunct to NSAIDs—for the treatment of OA have been conducted in humans, dogs, or cats. However, a neuropharmacologic rationale exists for gabapentin’s ability to diminish central and peripheral sensitization, which is supported by a number of rodent studies.^{17,18}

One canine study suggests that gabapentin may provide a chondroprotective effect in experimentally induced OA,¹⁹ and a pending study in cats appears to demonstrate the clinical efficacy of gabapentin for pain associated with naturally occurring feline hip OA.²⁰

Macrostability: Gross subluxation

Microstability: Diminished laxity of joint that cannot be grossly appreciated

Diagnostic & Treatment Considerations for OA Patients

- **Perform diagnostics.**
- **Conduct** a thorough history, physical examination, imaging, and laboratory evaluation.
- **Establish treatment goals** with the owner, and then create the treatment plan.
- **Explain that the reward for the pet** can be great in terms of longevity and improved quality of life, but only with good cooperation, compliance, and communication.
- **Educate owners on how to recognize potential drug adverse events.** Explain what to do if adverse events occur.
- **Follow-up.** Schedule the next reassessment before the client leaves. Touch base periodically with one of the validated chronic pain/disability owner assessment tools.

Amantadine

One study in dogs with refractory OA demonstrated the efficacy of amantadine and an NSAID versus NSAIDs alone.²¹

Tramadol

The pharmacokinetics of oral tramadol do not favor its use for OA pain in dogs.²²⁻²⁵ In fact, the pharmacokinetics of oral tramadol are not favorable in the dog, in general, and especially not for chronic use (plasma levels, low to begin with, diminish rapidly to near negligible levels after sequential use over several days). Even with IV tramadol, dogs do not produce the mu receptor active metabolite that occurs in humans.²⁶ It may be better suited pharmacologically for cats,²⁷ but its extremely bitter taste may limit its use.

At this time, no studies have been published that demonstrate tramadol's efficacy for treatment of OA in cats or dogs, either alone or as an adjunct to NSAIDs. The results of one canine study suggested that dogs with OA improved with tramadol according to owner assessments; however, the placebo group also improved, and there was no improvement in the tramadol group according to objective gait analysis.²⁵ However, one study submitted for publication may reveal more encouraging results.²⁸

The Role of Constant Rate Infusions

Intravenous constant rate infusions (CRI) of ketamine, lidocaine, opioids, or a combination can be used for a 24 to 48 hour *pain holiday* and to also reduce central sensitization. Used for severe neuropathic pain states in humans, this methodology has been anecdotally used but not yet investigated in canine and feline patients with OA.

Tricyclic Antidepressants & Selective Serotonin/Norepinephrine Reuptake Inhibitors

Although known for their ability to treat chronic and neuropathic pain conditions in humans, as of yet, no data support the use of these drugs for management of canine or feline OA.

- Duloxetine (Cymbalta, lilly.com), a selective serotonin/norepinephrine reuptake inhibitor, is labeled for musculoskeletal and low back pain in humans, but has very poor oral bioavailability in dogs.²⁹
- Oral venlafaxine (Effexor, pfizer.com), labeled as an antidepressant in humans, has been demonstrated to diminish pain intensity and improve function in humans with OA.³⁰ In dogs, it has approximately 50% bioavailability and a half-life of 3 hours.³¹
- There is no strong evidence for the pain modifying effect of fluoxetine, a selective serotonin reuptake inhibitor.

Corticosteroids

Intra-articular corticosteroid injection is a first-line therapy for OA in humans and horses. In dogs, studies in experimentally induced OA demonstrate that corticosteroid injections may have a disease modifying and, possibly, chondroprotective effect,³²⁻³⁵ but clinical studies are lacking.

Acetaminophen

Acetaminophen remains a first-line therapy for acute and chronic pain in elderly humans,³⁶ and unlike cats, a literature search for toxicity in dogs does not reveal any special sensitivity to adverse effects or toxicity in this species. Judicious use can be considered in dogs but not in cats.

Oral Opioids

Dogs have a robust first-pass effect with oral opioids, limiting their usefulness compared with human patients, but pharmacokinetic studies reveal the possible efficacy of codeine³⁷ and hydrocodone³⁸ in this species.

Nonpharmacologic

Nonpharmacologic treatment of OA in dogs and cats includes a variety of therapies (Table 3, page 29). While unsupported at this time by strong clinical evidence, these modalities:

- Have plausible, if yet unproven, beneficial effects
- Are generally safe with proper use
- May be employed as an adjunct to other therapies, or when nonpharmacologic modalities are indicated or preferred.

As part of an integrated approach to treating pain, acupuncture, in particular, has been accepted by both the National Institutes of Health (nih.gov) and International Veterinary Academy of Pain Management (ivapm.org) in their respective position/consensus statements.

Biologic

The relative merits and roles of intra-articular stem cell therapy, platelet-rich plasma therapy, extracellular matrix bioscaffolds, hyaluronate, and even botulinum toxin remain areas of interest and research. How these modalities will fit into management of OA remains undetermined at this time.

One commercial autologous conditioned serum product (IRAP, arthrexvetsystems.com) is labeled for intra-articu-

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TABLE 2. Recommended Doses for Pain Modifying Analgesic Drugs

	SUGGESTED DOSE	PRIMARY ADVERSE EFFECTS & NOTES
Acetaminophen	10–15 mg/kg PO Q 12 H ³⁹	<ul style="list-style-type: none"> Contraindicated in cats No special proclivity toward hepatotoxicity in dogs; judicious use recommended
Amantadine <i>NMDA receptor antagonist</i>	3–5 mg/kg PO Q 12 H ²¹	<ul style="list-style-type: none"> Primary adverse effects include agitation and diarrhea Anticholinergic
Amitriptyline^a <i>Tricyclic antidepressant</i>	<i>Dogs, initial dose:</i> 1–2 mg/kg PO Q 8–12 H ³⁹ <i>Increase as needed to:</i> 3–4 mg/kg PO Q 8–12 H ²⁹	<ul style="list-style-type: none"> Primary adverse effects include, in humans, dry mouth, sedation, behavioral changes, and seizure potentiation
Codeine^b <i>Opioid</i>	0.5–2 mg/kg PO Q 12 H ³⁹	<ul style="list-style-type: none"> Some suggest dogs only Pharmacokinetics, but no clinical data, available
Gabapentin <i>Anticonvulsant</i>	Initially 3–5 mg/kg PO Q 12 H, taper upwards to effect; doses as high as 20 mg/kg or more may be needed PO Q 8–12 H ³⁹	<ul style="list-style-type: none"> Primary adverse effects include somnolence, which can be minimized by starting with lower doses and gradually increasing to effect For smaller animals, may be compounded into 50 mg/mL nonxylitol containing suspension
Hydrocodone^b <i>Opioid</i>	0.22–0.5 mg/kg PO Q 8–12 H ³⁹	<ul style="list-style-type: none"> Some suggest dogs only Pharmacokinetics, but no clinical data, available
Morphine/lidocaine/ketamine CRI	<i>Dogs:</i> Morphine, 4 mcg/kg/min Lidocaine, 50 mcg/kg/min Ketamine, 10 mcg/kg/min CRI for 24–48 H	<ul style="list-style-type: none"> Primary adverse effects include sedation Clinical utility for chronic <i>pain holiday</i> anecdotal only Administer combined or individually
Tramadol^a	<i>Cats:</i> 1–4 mg/kg PO Q 12 H ³⁹ <i>Dogs:</i> 2–10 ^c mg/kg PO Q 8–12 H ²⁹	<ul style="list-style-type: none"> Primary adverse effects include, in humans, GI effects, behavioral changes, seizure potentiation, hypertension, bleeding dyscrasia, sedation Unfavorable pharmacokinetics in dogs; better in cats No safety or toxicity data in dogs or cats; limited to no data to support efficacy in dogs Higher doses may increase risk for adverse effects
Venflaxine^a <i>SSNRI</i>	3–4 mg/kg PO Q 8–12 H ³¹	<ul style="list-style-type: none"> Not in clinical use for chronic pain in dogs or cats No safety or toxicity data

a. Caution should be exercised when using these and other serotonergic, monoaminergic drugs in combination.

b. If used in combination with acetaminophen, base dosage administered on calculated acetaminophen dose.

c. Higher doses are more likely to lead to adverse effects, and it is prudent to initiate dosing at 2–4 mg/kg.

NMDA = N-methyl-D-aspartate; SSNRI = serotonin-norepinephrine reuptake inhibitor

lar injection in horses with OA; it suppresses the highly pro-inflammatory cytokine Interleukin-1. There is no similar commercial product for use in dogs, but there is indication that the modality may have a disease-modifying effect in this species.⁴¹

A commercial systemically administered anti-nerve growth factor monoclonal antibody product is currently in development for the treatment of canine OA. Investigations are also in progress for treatment of canine OA with Interleukin-10, a potent inhibitor of spinal cord glial activity.

IN SUMMARY

The ideal pain management protocol for a particular OA patient will vary by stage of disease, doctor and client values, and of course, individual needs and responses. ■

TABLE 3. Common Nonpharmacologic Therapies for Canine & Feline OA

- Acupuncture
- Myofascial trigger point therapy
- Therapeutic laser (photobiomodulation)
- Pulsed acoustic wave therapy
- Pulsed electromagnetic field therapy

COX = cyclooxygenase; CRI = constant rate infusion; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; PSGAG = polysulfated glycosaminoglycan

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