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Expert Views from a Roundtable on Canine Osteoarthritis

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Canine Osteoarthritis: Optimizing Diagnosis and Disease Management

Managing OA in dogs continues to present a challenge. Among the issues that the veterinarian faces is the need to recognize the disease early—and educate the owner that intervening at the outset of clinical signs is warranted. Other challenges include instituting effective control of pain and inflammation and balancing this with potential side effects of chronic or long-term therapies. This expert panel addresses the current state of the art in detecting and treating OA.

Dr. Ryan: What do we know about canine OA today that we didn't know 5 years ago?

Dr. Perkowski: We better understand the progressive nature of the disease and the importance of starting treatment early, before the appearance of clinical signs that an owner might recognize. And we know that it's a multifactorial disease.

Dr. Kirkby Shaw: Now we recognize OA as a whole-body disease. From a treatment standpoint, we are going to address the entire body, not just the joint that is affected.

Dr. Lascelles: As a profession, we are not good at identifying early signs of OA. They are there, but they're not obvious because these dogs are still moving and are relatively happy. But if you look carefully, many dogs with developmental disease are working really hard to avoid using painful joints. Even subtle changes in body carriage involve a lot of work by the individual animal, indicating a significant problem the pet is trying to avoid. Additionally, we now know that dogs with OA can develop central sensitization quickly after the onset of pain.

Dr. Ryan: How does OA impact the dog's overall health and how does this vary by OA stage?

Dr. Lascelles: Across the stages you've got progressive deterioration of the musculoskeletal system. (See ***Table***,

ABBREVIATIONS

CBPI	Canine Brief Pain Inventory
CMI	Clinical metrology instrument
CODI	Canine Orthopedic Disability Index
COX	Cyclo-oxygenase
CSOM	Client-specific outcomes measures
DJD	Degenerative joint disease
EP	Prostanoid receptors sensitive to prostaglandin E_2
EPA	Eicosapentaenoic acid
GI	Gastrointestinal
LOAD	Liverpool Osteoarthritis in Dogs
MAP	Mitogen-activated protein
NF-kB	Nuclear factor kappa-light-chain enhancer of activated B cells
NSAID	Nonsteroidal anti-inflammatory drug
OA	Osteoarthritis
PG	Prostaglandin
PRA	Prostaglandin receptor antagonist
PSGAG	Polysulfated glycosaminoglycan
TXA	Thromboxane

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The cornerstone of treatment is the alleviation of pain, and I am adamant that it needs to be addressed using predictably efficacious analgesics.

—Dr. Lascelles

This roundtable was conducted before the widespread incorporation of Galliprant® (grapiprant tablets) into practice since its release in January 2017. Participants have since benefitted from more than a year of experience, which appears to confirm the drug's safety and efficacy, as shown in the pivotal studies.

below.) The muscle tension associated with the pain and progressive muscle atrophy that's most obvious in one limb will progress to other parts of the body. You've also got progressive deterioration of the somatosensory system across those stages. The final thing, which we do not really appreciate or understand, is the cognitive decline, anxiety, and fear that are happening progressively throughout these stages.

Dr. Epstein: It is critical to understand the consequences of under-recognized and under-managed OA. As the disease progresses, dogs are increasingly unable to engage in their normal daily activities, which can have a substantial impact on their lives. OA is a multifaceted, multidimensional, progressive disease that requires intervention with a multimodal treatment approach, preferably early in the process.

Dr. Perkowski: Chronic inflammation sets up throughout the whole body. It's not just a single joint, it's a whole-body disease. It's important to decrease inflammation early.

Assessing for OA

Dr. Ryan: Do you use CMIs to help with OA diagnosis?

Dr. Kirkby Shaw: We use a CMI for patients that come in through the rehab service. From day 1, they complete the CMI to start with an objective point in time. Then we put together a plan and have the clients fill it out regularly.

Dr. Epstein: The CODI is done by interview. It doesn't measure pain but rather abilities and disabilities, which are progressive. An advantage to the CODI is that we can get an update over the phone. The CBPI is now used by the FDA to measure the efficacy of new OA products. This is what we're using now as an outcome measure rather than the force plate.

TABLE

STAGES OF CANINE OSTEOARTHRITIS

Stage	Description
1	At-risk dogs; an observant, trained veterinarian can detect clinical signs; a perceptive owner also might notice signs
2	Intermittent, obvious signs (eg, a "weekend warrior" type); obvious impairment of ability to perform certain daily activities that often triggers a visit to the veterinarian; consistent, obvious alterations in body carriage and the beginnings of apparent muscle loss
3	Consistent impairment of form and diminished capacity to engage in activities of daily living
4	Mobility impairment; clearly diminished ability to move or jump relative to previous normal activity

Dr. Lascelles: The off-the-shelf CMIs take less than 2 minutes to complete by the owner and can be done in the waiting room. We use the LOAD, which is the most responsive of these CMIs, in combination with a goal attainment scaling approach like the CSOM questionnaire.

Dr. Kirkby Shaw: The force plate and the CBPI are measuring two separate things. If we are looking at a whole-body disease that is measured by the dog's change in function and behavior (what chronic pain is measured by), we should use a validated CMI such as the CBPI. To assess weight bearing through an individual limb, the force plate is a more valuable tool.

Dr. Ryan: If you have an owner who is reluctant to do a full workup, what is your go-to diagnostic test for OA?

Dr. Kirkby Shaw: My best diagnostic tool is my orthopedic exam, which begins by taking a thorough history, then watching the dog move around the exam room and studying its transitions (down to stand, stand to sit, etc) before I ever touch it. I also rely on palpation to assess muscle symmetry and soft tissue structures remote from the joints.

Dr. Perkowski: I also palpate the spine along either side of the back and neck.

Dr. Lascelles: Observation first, then orthopedic evaluation. I observe the dog's resting position, standing position, body carriage, and the way it moves; that almost tells you everything you need to know. With the orthopedic evaluation, muscle atrophy is the most important aspect.

Dr. Epstein: The lumbosacral joint is often affected. It won't be apparent unless you actually perform dorsoflexion of the tail while applying digital pressure at the lumbosacral joint.

Educating the Owner

Dr. Ryan: If somebody brings a dog in that they think is normal but you've determined the dog has OA, how do you communicate and educate an owner that the dog needs treatment?

Dr. Lascelles: I don't downplay the fact that I have made a diagnosis of OA or that I have a high suspicion, but I immediately follow up with the message that if we act aggressively now with a multimodal approach, we may help prevent problems in the future. You want to approach it in an optimistic way—not "Oh, your dog has OA; it's a lifelong disease. It's only going to get worse." We need to change that around but still communicate the gravity. I talk about a window of opportunity and ask them to work with me for 3 to 4 months. If you overemphasize that this is a lifelong disease with very little that can be done, you end up being overly pessimistic.

Dr. Kirkby Shaw: But what happens after 3 or 4 months? Do you follow up?

Dr. Lascelles: After those few months, they see the benefits. Most are on board for lifelong management.

Dr. Epstein: I'm in primary care, so these patients are usually coming in for an annual visit in which we learn that the dog has become symptomatic in subtle or more obvious ways. We talk about all of these other things in the 10 minutes that we have, but I tell the owners that everything I'm hearing and seeing tells me their dog is developing early signs of OA. I send them home with a trial of an anti-inflammatory and tell them I'll be in touch in a few days for them to tell me how the pet did with this medication. Then we map out a treatment plan that we'll continue to talk about for the rest of its life. **Dispensing that trial of an anti-inflammatory analgesic is like proof-of-concept that the dog is symptomatic for disease.**

Dr. Lascelles: If I see the signs and the client is not quite sure, then I will absolutely do that trial of an analgesic. But I will ask them to look at very specific things, such as the dog with a rounded back due to hip OA. I'll say, "Just watch that over the next few weeks and let's see if that rounded back flattens out. We'll try this and see what happens." It's 2 to 4 weeks of an analgesic, and they come back for a revisit. We talk about any adverse events and do another evaluation, possibly repeat blood work. If they're not responding to that medication, I switch to another.

Weight, Exercise, Rehab, & Pharmaceuticals

Dr. Ryan: What nonpharmacologic approaches do you use to see dogs through from mild through severe disease?

Dr. Lascelles: In younger dogs, I see these

My best diagnostic tool is my thorough orthopedic exam, which begins by taking a thorough history, then watching the dog move around the exam room and studying its transitions (down to stand, stand to sit, etc) before I ever touch it.

—Dr. Kirkby Shaw

It is critical to understand the end consequences of under-recognized and under-managed OA.

—Dr. Epstein

as preventive measures versus the therapeutic measures you take in the older dog. Across the stages, exercise moves from preventive into therapeutic, and the type of exercise varies across the different stages. Consistent, sustained exercise is critical—about 1 hour of leash-walking a day. **Sustained exercise is a great preventive.** For a therapeutic program, the underwater treadmill is useful. Use the water just to get them up and get the legs moving to reduce lameness and improve their ability to perform activities of daily living.

Dr. Epstein: We can't overemphasize weight management. Adipose tissue is the body's largest endocrine organ. Everything it secretes is nasty, and it bathes the body in a soup of pro-inflammatory cytokines. It accelerates or sustains the inflammation in the synovium, which increases the production of prostaglandins as well as catabolic enzymes, which speed up the degradation of cartilage.

Dr. Kirkby Shaw: For anyone who sees dogs with OA, it is important to recommend regular, controlled, low-impact exercises. Involving someone who is trained in canine rehabilitation can be very valuable. It is important that a *veterinarian* trained in rehabilitation establishes a whole-body rehab diagnosis and develops a customized plan for the individual dog. Veterinary technicians and human physical therapists certified in canine rehabilitation may also be involved in the care of dogs with OA. Underwater treadmill therapy, land based exercises, and other modalities will be used to help maintain mobility and functional independence.

Dr. Lascelles: What are your thoughts on the lifelong value of starting a consistent exercise regimen in young dogs?

Dr. Kirkby Shaw: In a young dog with open growth plates, it's beneficial to encourage normal puppy play but not running or high-impact jumping. You also want to establish the habit of walking, obedience training, and capturing certain behavioral traits, like sitting and standing at attention.

Dr. Perkowski: Because OA is progressive, it's important to start treating early and to think about weight management and exercise. Having good muscle mass helps stabilize the joints.

Dr. Ryan: How are medications initially incorporated in dogs with early OA?

Dr. Perkowski: For dogs showing early or intermittent signs of OA, I recommend initiating treatment rather than waiting until after the dog is limping.

Dr. Kirkby Shaw: Adequan® Canine (polysulfated glycosaminoglycan) is effective when started early in the OA disease process. I start dogs on it as soon as I have diagnosed OA. Ideally we are identifying early OA/DJD in young dogs with developmental orthopedic disease.

The Multimodal Treatment Approach

Dr. Ryan: What does your overall multimodal treatment plan look like for a dog with OA?

Dr. Epstein: I start off with NSAIDs. Weight optimization is also right up there, and from a preventive standpoint, it's probably the number one most important. I also reach for a disease-modifying osteoarthritis agent—specifically Adequan Canine, from an evidence-based perspective.* EPA-rich diets and therapeutic exercise are in there.

Dr. Perkowski: NSAIDs are the cornerstone, first line of defense.

Dr. Lascelles: The cornerstone of treatment is the alleviation of pain, and I am adamant that it needs to be addressed using predictably efficacious analgesics. Up until now, the only predictably efficacious class of drugs has been COX-inhibiting NSAIDs. Now we have a piprant that acts as a non-COX inhibiting NSAID. Weight management, diet optimization, exercise, keeping on top of the animal's level of discomfort—those are difficult conversations to have, and they're difficult for a practice to monetize.

Dr. Kirkby Shaw: It's important to watch a dog's weight and keep it active. Depending on the age of the dog, regular, controlled, low-impact exercise is absolutely crucial, ideally on a daily basis. **Weight loss, nutrition, and disease- modifying drugs take time to take effect, which is one of the reasons that NSAIDs are a cornerstone. And we need to get on top of pain as soon as we can, to try and avoid central sensitization.** With an NSAID, we can have a result within 24 hours in many cases, especially for dogs that are clinically affected.

Dr. Perkowski: But you don't want to overwhelm the owner. They are going to hear the first 3 things you tell them and everything thing else will go out the other ear.

Dr. Epstein: I follow up with an email.

Dr. Lascelles: There is great opportunity for creating educational materials. The veterinarian can provide them in a way that the owner perceives as the veterinarian adding value to the relationship. An interactive digital platform can also connect the owner and the veterinarian.

Dr. Kirkby Shaw: As a profession, we need to bring client education back to us instead of coming from the pet food store or the trainer or the Internet. We really need to bring that value back into the veterinary clinic.

The Value of Analgesics

Dr. Ryan: You've mentioned that NSAIDs are a key aspect of OA treatment. What are your thoughts on intermittent versus continuous NSAID dosing?

Dr. Epstein: There's convincing evidence for the advantage of continued dosing over intermittent doses. In 2 separate studies with dogs getting daily doses of NSAIDs over 6 months and a year, they kept getting better over that entire time.[1,2] It's not just a matter of reducing inflammation; you're also reducing peripheral and central sensitization that arises as a consequence of chronic inflammation.

Dr. Kirkby Shaw: The Galliprant® (grapiprant tablets) trial data support that. If you look at the results of the CBPI, dogs on the study drug (Galliprant) showed continued statistically significant improvement at 7, 14, 21, and 28 days.† In other words, dogs continued to show improvement over the entire month studied.[3]

Dr. Lascelles: Yes, if there is pain the treatment should be prolonged—which means daily, approved doses of an effective analgesic. But we also have to remember that everything is plastic and that plasticity can go in both positive and negative directions. We talk about central nervous system plasticity and central sensitization, but the musculoskeletal system is also plastic. As you provide that pain relief, you may have the opportunity to reduce the dose of analgesic.

Dr. Epstein: For the symptomatic patient, there is evidence that daily doses given long-term seem to be advantageous over using them intermittently.[1,2]

Dr. Perkowski: If you're going to see an adverse event with an NSAID, it typically happens within the first few weeks. It doesn't necessarily mean you're going to have one with another nonsteroidal. Most likely, I wouldn't keep a dog on a full label dose for a year, even though there is a paper that says it's okay. I would like it to be at the lowest dose necessary to provide the changes I'm looking for—and that's not just pain. It might be effusion in the stifle or other signs of inflammation.

Consequences of OA

Dr. Ryan: What are the consequences of waiting to treat patients until the OA is advanced?

Dr. Lascelles: When I see dogs with advanced OA, there is often significant deterioration of the musculoskeletal system, the sensory system, and the affective system (fear, feeling, anxiety). I often think that earlier treatment would have benefited these patients.

† Primary study endpoint

There's convincing evidence for the advantage of continued dosing over intermittent doses. In 2 separate studies with dogs getting daily doses of NSAIDs over 6 months and a year, they kept getting better over that entire time.[1,2]

—Dr. Epstein

Since its release, I have been choosing Galliprant® (grapiprant tablets) as a first-line option for OA cases.

—Dr. Kirkby Shaw

Dr. Perkowski: As OA progresses, destructive metalloproteinases and other inflammatory cytokines and prostaglandins are produced in the joint.

Dr. Kirkby Shaw: It's much harder to treat once chronic pain has set in.

Dr. Perkowski: **Treating OA early is a real game-changer.** It takes your analgesia protocol to the next level. Galliprant provides another treatment option for veterinarians that can be used as soon as OA is diagnosed.

Dr. Lascelles: **The goal of a multimodal treatment plan is to prevent that cycle of deterioration from being initiated and getting a grip.** Once that has started, it's really difficult to pull them back. Galliprant is one option that might make veterinarians feel comfortable about treating pain early.

Dr. Ryan: **So one of the benefits of Galliprant is that it's a good tool that veterinarians can use to treat OA early?**

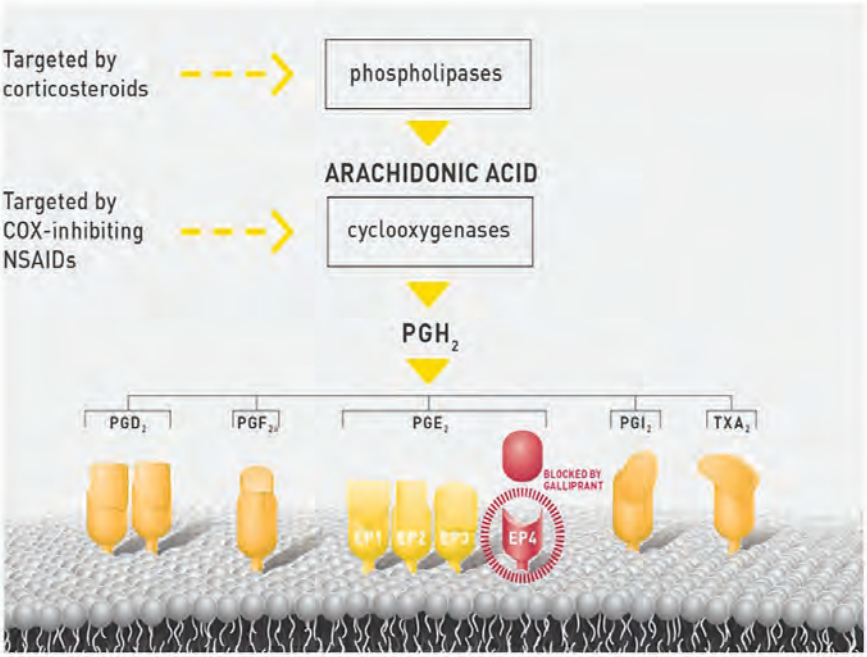
Dr. Epstein: We are veterinarians and we, above all, want to do no harm, but **that mindset has created a circumstance where we're undermanaging pain because of our perceptions of risk and not managing in such a way that maximizes the benefit for the patient**. All treatments have side effects that must be considered when prescribing a chronic OA medication. Galliprant, a non-COX inhibiting NSAID that specifically antagonizes the PGE_2 EP4 receptor, may give us the confidence to do what we should.

Dr. Lascelles: There is this embedded fear of treating OA in young dogs, particularly with prescription products intended for chronic use.

The goal of a multimodal treatment plan is to prevent that cycle of deterioration from being initiated and getting a grip. Once that has started, it's really difficult to pull them back. Galliprant is one option that might make veterinarians feel comfortable about treating pain early.

—Dr. Lascelles

Galliprant Mode of Action



See important safety information on page 5.

Dr. Perkowski: The nonsteroidals are a heterogeneous mix of molecules that are grouped together and most inhibit the COX enzymes. Galliprant is a non-COX inhibiting PRA NSAID that specifically targets the EP4 receptor downstream of these enzymes.

Dr. Epstein: The EP4 receptor is largely but not exclusively responsible for the pain and inflammation of OA. The EP1, EP2, and EP3 receptors are largely but not exclusively responsible for gastrointestinal and renal homeostasis. That's why a downstream action can target pain and inflammation while reducing the impact on GI, kidney, and liver homeostatic functions that are mediated by PGE_2.

Dr. Lascelles: I agree with all of those comments. The ability to treat pain associated with OA early and chronically is beneficial. One of the exciting things about Galliprant is that it can do both.

Dr. Ryan: NSAIDs are known for their GI effects. What are the implications for veterinarians prescribing Galliprant for OA treatment?

Dr. Kirkby Shaw: The most commonly reported adverse reactions in the pivotal field trial were anorexia, inappetence, diarrhea, soft stools, and vomiting. Vomiting is one of the most common side effects for all NSAIDs, including Galliprant. With Galliprant, this isn't thought to be a pathologic process in the stomach or duodenum. It's potentially a motility issue, based on the mechanism of action of the PGE_2 EP4 receptor.[6]

Dr. Epstein: As a clinician, if you have a patient on a COX-inhibiting nonsteroidal, you tell the owner to stop the drug and call you if the dog vomits. Then you probably put the dog on some gastroprotectant out of an abundance of caution. Maybe the vomiting was due to the NSAIDs, maybe not.

Dr. Ryan: Do you have owners call you after just a single occasion of vomiting?

Dr. Epstein: Yes, but it seems that you don't necessarily need to withdraw Galliprant if vomiting occurs.

Dr. Kirkby Shaw: As I gain experience with this new product, I do ask my clients to call if any vomiting occurs, but I do not necessarily discontinue Galliprant. The Galliprant client insert doesn't say anything about contacting your vet or stopping the medication for vomiting. It does say to call if there is a change in stool consistency or appetite, but it doesn't say to stop the medication.

Dr. Lascelles: Even with Galliprant, if there is vomiting, I proactively ask the owner to call me. If it's a single episode and the dog is bright, alert, eating, and drinking, I will probably continue with the Galliprant. If there have been a couple of episodes of vomiting, I will probably stop the drug and reintroduce it 2 days later. I feel better about keeping the drug going, but I'm still going to take what I consider a sensible approach to it. I have seen no reason to use gastroprotectants under those circumstances.

Dr. Kirkby Shaw: EP4 is not involved in acid secretion in the stomach, so giving an antacid is probably not going to make a big difference.

Dr. Ryan: Where are you using Galliprant? In what patients?

Dr. Kirkby Shaw: Since its release, I have been choosing Galliprant as a first-line option for OA cases. I have also switched dogs that were intolerant of other NSAIDs to Galliprant.

Dr. Epstein: I am using Galliprant primarily as a first-line therapy, but I'm also including OA patients assessed as intolerant to other NSAIDs for one reason or another.

Dr. Lascelles: Yes, my preference is to use it in ever-expanding circles within my OA patient population. So I'm starting with regular OA cases, the dogs in which I would use NSAIDs. Once I get comfortable there, I will then expand out to other OA patients, cases that may be considered higher risk for traditional COX-inhibiting NSAIDs.

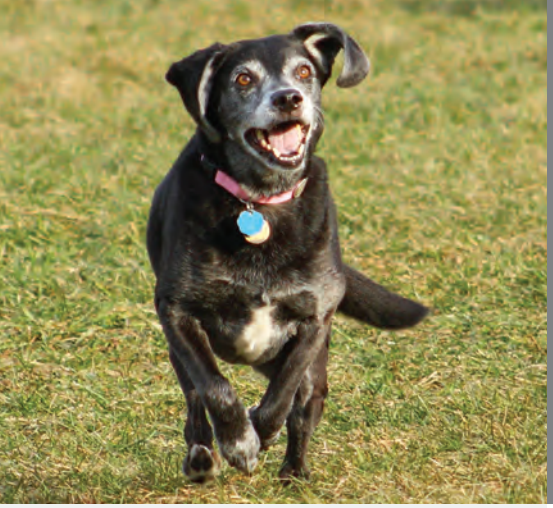
Dr. Perkowski: I'm trying it in patients in which I might have normally used a COX-inhibiting NSAID and seeing what the efficacy is like.Once I get to a certain comfort level, I may start to expand my use to other OA cases.

See important safety information on page 5.

Select Important Safety Information
Do not use in dogs that have a hypersensitivity to grapiprant. If Galliprant is used long-term, appropriate monitoring is recommended. Concomitant use of Galliprant with other anti-inflammatory drugs, such as COX-inhibiting NSAIDs or corticosteroids, should be avoided. **See additional important safety information on page 5.**

Treating OA early is a real game changer. It takes your analgesia protocol to the next level.

—Dr. Perkowski



As a first-in-class, non-COX inhibiting PRA NSAID, Galliprant® (grapiprant tablets) is the next generation of OA pain management. This is taking it to the next level. The future is here.

—Dr. Perkowski

Dr. Ryan: What does Galliprant mean for the future of OA treatment?

Dr. Kirkby Shaw: This is the first time in 20 years that we have an NSAID with a new mechanism of action. We now have this targeted effect that is sparing all of the prostanoids (prostaglandin E, I, D, F2 alpha, and thromboxane) and allowing them to maintain their homeostatic roles throughout the body. We can target the one receptor that's most important in transmitting pain and inflammation—the one shown to be upregulated in the joint and the dorsal root ganglion in chronic pain states.[7]

Dr. Epstein: From an evidence-based perspective, nonsteroidals occupy the top tier in terms of a quick and predictable response. On the other hand, we're not intervening early enough. We're not using NSAIDs as aggressively as the evidence suggests we should be, because we fear adverse events. With Galliprant we have a new NSAID class that should give us confidence to alleviate pain and inflammation in a way that we know will benefit patients.

Dr. Perkowski: As a first-in-class, non-COX inhibiting PRA NSAID, Galliprant is the next generation of OA pain management. This is taking it to the next level. The future is here.

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