MANAGING THE CHRONIC PAIN AND DYSFUNCTION OF OSTEOARTHRITIS

Objectives

1. **To have an understanding of the physiological effects of pain on the body**
2. **Review the therapies currently used to treat OA in dogs and cats**
3. **Review the peer-reviewed literature to support your treatment decisions**

The Price of Pain

The practice of identifying pain and implementing an appropriate pain management strategy is an ongoing struggle and a source of significant frustration for the small animal clinician. Historically, the development of recognition methods and assessment of animal pain has been delayed by the reluctance of some people to believe pain is a significant clinical problem in our patients. Thankfully the days of "keeping them in some pain to stop them for doing too much" are gone. It is now clear that untreated pain is highly detrimental to our patients. While there has been an improved effort to identify painful situations and then treat them appropriately, there is little focus on the potential physical alterations that occur in these patients. Unfortunately, there is minimal hard scientific data to quantify these changes that occur in our veterinary patients. Thus, this lecture will encompass data from multiple species and try to provide a rationale for providing aggressive pain management to our patients. Although physiological and behavioral changes are used here to define the presence and intensity of the experience, more studies are required to determine which changes to measure and how this can be achieved so that they can be applied to individual animals under clinical conditions.

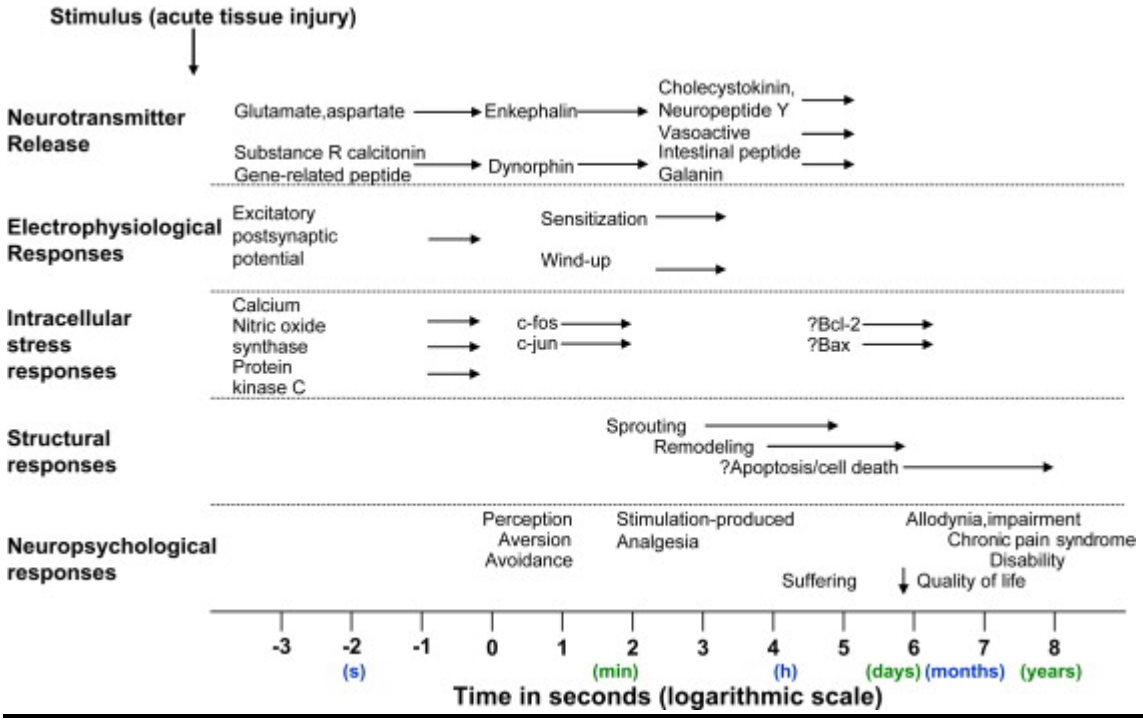
Alterations in Physiology - Acute and chronic pain are accompanied by a neurohumoral response that can have a significant negative impact on our patients (Figure 1). In response to the stress of trauma and pain, increased release of catecholamines can lead to tachycardia, elevated blood pressure, and associated myocardial oxygen utilization. This may result in left ventricular dysfunction, myocardial ischemia, or myocardial infarction. Other hormones released in response to the stress of untreated pain include cortisol and glucagon. These hormones can lead to insulin resistance, hyperglycemia, alterations of protein and fat metabolism, and postoperative complications. Stress associated with inadequately treated acute pain can produce hypercoagulability and impaired activity of both innate and adaptive immunity. The consequences of these changes may include venous thromboembolic disease and increased risk of postoperative infections. Early studies have demonstrated that, when pain is adequately treated, the magnitude of these perioperative neurohumoral and hemostatic changes is diminished.

Clinical Manifestations - In addition to metabolic, hemodynamic, and hemostatic changes, inadequately treated pain can produce impairments that are more clinically obvious, although not necessarily more clinically significant. Postoperative pain with thoracic and abdominal splinting can impair respiratory excursions, sometimes inhibiting coughing needed to clear the airway and prevent atelectasis. Furthermore, inadequately treated acute pain can delay return of normal gastrointestinal function. The same increased autonomic outflow can contribute to postoperative urinary retention. Unmanaged, acute postoperative pain can also delay mobilization, which can increase the risk of venous thromboembolic disease, produce joint stiffness, and delay rehabilitation. While it is known in humans that inadequate acute pain management can have significant psychosocial consequences, we are unsure if the same is true in our patients. Similarly, people with unrelieved postoperative pain can be anxious, agitated, and are unable to sleep well. Certainly, as clinicians we have all seen these signs in our patients. With persistent chronic pain, less data is available to assess the negative outcomes. In humans, the literature supports that poorly controlled postoperative pain is a risk factor for the development of chronic pain; however, it is not necessarily causative. The mechanisms by which acute pain leads to a chronic pain state is depicted in the complex cascade of events that occur when tissues are initially injured (Figure 1).

Osteoarthritis (OA) and pain – An example of chronic pain we all deal with frequently is osteoarthritis. What are the consequences to the body of this chronic painful situation? Honestly, we just don't know. We do know that if persistent, maladaptive chronic pain should be considered an ongoing disease process. Thus, we should treat OA pain as an active disease process and aggressively try to alter its' negative influences on the body. This is no easy task as OA pain involves a complex integration of sensory, affective, and cognitive process that integrate a variety of abnormal cellular mechanisms at both peripheral and central (spinal and supraspinal) levels. The role of growth factors and cytokines has increasingly become more relevant in the understanding of the development of AO-associated pain. Therefore, our plans about effective treatment need to focus on the catabolic and nociceptive stimulating factors (IL-1, IL-6, TNF-α, PGE-2, FGF-2 and Protein Kinase C alpha [PKCα]), which are released in chronic OA and pharmacologic inhibitors to these compounds. However, as clinicians most of us don't have the time or energy to work on these problems. We often wonder whether the treatments we are giving are too toxic (NSAIDs) or too expensive to continue them if the dog or cat does not appear to be severely affected. Well, let us look at an example from human medicine. In people, studies have look at the effects of fibromyalgia on daily activities. Gait analysis studies have shown walking speed, stride length, and step regularity was diminished or more poorly controlled when compared to matched controls. Overall a reduced walking speed, decreased stride length, and swing phase were found as well as increased oxygen cost and consumption. These data suggest that compensation is costly to the body and is due to decreased levels of physical activity, increased body weight and overt pain. These end stage factors are very familiar to us and so it is clear we must continue to manage this pain and dysfunction as aggressively as we can in our patients.

In summary, there is ample data from the literature that not choosing to treat or to undertreat our patients for either acute or chronic pain states may lead to significant negative physiological changes in our canine and feline patients.

Figure 1 – Example of responses with an acute injury and then the potential carryover into the chronic situation.



REVIEW OF THERAPIES FOR THE TREATMENT OF OSTEOARTHRITIS (OA)

While considered a very common problem in small animal medicine, osteoarthritis is very likely the most under diagnosed and misunderstood rheumatic disease in dogs and cats. Part of the problem veterinarians face with OA is that it is a slow, progressive, and often insidious problem. In the dog, primary OA is uncommon and OA development always occurs secondary to another joint pathology. The wide range of clinical signs makes OA a commonly misdiagnosed condition. Osteoarthritis has been estimated to affect 20% of the U.S. canine population. This widely referenced estimate, in practical terms, translates to over 10 million dogs. No realistic estimate has ever been made about the number of cats affected. Thus, the identification and management of the disease is of the utmost importance to the small animal clinician.

Osteoarthritic diseases are a result of both mechanical and biologic events—ones that destabilize the normal coupling of degradation and synthesis of articular cartilage chondrocytes, extracellular matrix (primarily collagen and aggrecan), and subchondral bone. Although these events may be initiated by multiple factors, including genetic, developmental, metabolic, and traumatic factors, osteoarthritic diseases involve all of the tissues of the diarthrodial joint. Ultimately, osteoarthritic diseases are manifested by morphologic, biochemical, molecular, and biomechanical changes of both cells and matrix, which lead to softening, fibrillation, ulceration, articular cartilage loss, sclerosis and subchondral bone eburnation, and osteophyte production. When clinically evident, osteoarthritic diseases are characterized by joint pain, tenderness, limitation of movement, crepitus, occasional effusion, and variable degrees of inflammation without systemic effects.

Pathophysiology - Osteoarthritis is characterized by articular cartilage degeneration and changes in the periarticular soft tissues (synovium and joint capsule) and subchondral bone. Specifically, the pathologic changes of osteoarthritis encompass articular cartilage degeneration, which includes matrix fibrillation, fissure appearance, gross ulceration, and full-thickness loss of the cartilage matrix. This pathology is accompanied by hypertrophic bone changes with osteophyte formation and subchondral bone plate thickening. Failure to repair the damage affecting the surface cartilage is a distinctive condition of OA. Failure of chondrocytes in injured articular cartilage to restore a functional matrix, in spite of high metabolic activity, remains a complex and challenging problem. What this says to the clinician is that, at the present time, there is no treatment regimen proven to arrest or reverse the cartilage degeneration.

Treatment Goal - Current therapy is primarily palliative, aiming to reduce pain and inflammation, and maintain or improve joint function, without altering the pathologic process in the tissue. Remember, most OA in the dog and cat is secondary to some other pathologic state, and thus the underlying cause must be identified in an attempt to minimize the long-term effects. Certainly efforts are being made to provide treatments which may alter the course of the disease but these therapies are still to a large part unproven.

Treatment Plan - Management of OA should be thought of as a multi-step approach with four to five important components. While some clinicians tend to reach for pharmacologic management alone, this is usually unsuccessful without concurrent management of exercise and weight reduction. Thus, starting to treat a patient with OA requires a lengthy discussion of all aspects of management with the client. Our discussion will follow the typical pattern we use in our practice. Remember, one must examine each case differently, assessing the age, normal activity levels, and, most importantly, the owner's expectant activity levels of the animal. Success largely depends on the accurate assessment of the client’s expectations for the pet.

- Weight reduction
- Nutritional support

- Exercise modification
- Physical therapy
- Pharmacologic
- Alternative Methods

CRITICAL ASSESSMENT OF THERAPIES FOR THE TREATMENT OF OSTEOARTHRITIS

How do we evaluate available information for its validity and applicability?

Some basic questions need to be answered for every type of study you read:

1. Are the methods and thus the results of the study valid?
2. How strong is the data presented – Study Type and Design
3. What are the results?
4. Will the results help in treatment of my patients?

It is important to understand the concept of a hierarchy of evidence. While every piece of evidence arising from clinical research is important, there are intrinsic quality differences that allow us to determine that some evidence is stronger and can help us determine the best care for our patients.

Weight Loss -What data is available to us?

There are several studies that provide data to support improved quality of life and lameness in the dog. The data for all is of moderate quality. An overall rating of the strength of the evidence concludes that one can have a moderate level of comfort with the results of the aforementioned studies that weight loss is recommended in the treatment of the pain associated with OA in dogs.

Nutritional Support (Functional Foods) - What data is available to us?

High N3 fatty acid ratio diets – Three level-I clinical trials using a diet high in N-3 omega (EPA and DHA) fatty acids. These studies identified improved effects on clinical signs associated with OA in dogs. An overall rating of the strength of the evidence concludes that one can have a moderate to high level of comfort with the results of the aforementioned studies that these diets are recommended in the treatment of the pain associated with OA in dogs.

Cats - One Level-I study. Limited positive outcome data. Very limited data to support use for OA pain in cats.

Exercise/Physical Therapy - What data is available to us?

There are limited studies that examine the effects of exercise on clinical dysfunction associated with OA in dogs. The data for all range from low to moderate quality. An overall rating of the strength of the evidence concludes that one can have a low to moderate level of comfort with the results of the aforementioned studies that PT is recommended in the treatment of the pain associated with OA in dogs.

Cats – No clinical data available.

Pharmacologic Management – What data is available to us?

NSAIDs

There are multiple studies to support the efficacy of NSAIDS for the treatment of OA in dogs. An overall rating of the strength of the evidence concludes that one can have a high level of comfort with the results of the aforementioned studies and strongly supports the use for OA pain in dogs.

There are also several studies (primarily with meloxicam) that demonstrate decreased pain and dysfunction in cats. An overall rating of the strength of the evidence concludes that one can have a moderate to high level of comfort with the results of the aforementioned studies and supports the use for OA pain in cats.

ADEQUAN

One Level I trial that showed possible short-term benefit. No data on long term repeated usage (Off label). Data provides a moderate level of comfort with the results of the aforementioned study that supports short-term (label) usage.

Cats – No clinical data available.

AMANTADINE

One Level I trial used as an adjunct to an NSAID (meloxicam) in dogs. Data showed more improvement than an NSAID alone. Results provide a moderate support of use in OA pain, only as an adjunctive therapy with NSAIDs.

Cats – No clinical data in the treatment of OA.

TRAMADOL

One single study in dogs with OA evaluating the effects of oral tramadol as a monotherapy. The study showed no improvement over placebo or baseline during the administration of tramadol. The data is of high quality. An overall rating of the strength of the evidence concludes that one can have a moderate level of comfort with the results of the aforementioned study does not support the use of tramadol in dogs with OA as a monotherapy.

Several studies, all Level –II were found in cats. They were all small samples sizes giving a low to moderate strength of evidence. However, given that there are conflicting results, the data prevents strong support the use of in cats.

GABAPENTIN

There are no available clinical studies evaluating the role of gabapentin in treatment of OA in dogs. No data to support use in the dog.

In cats, one level II study found improvement but also noted the cats were more sedate and less active? The data for all is of low to moderate quality. An overall rating of the strength of the evidence concludes that one can have a moderate level of comfort with the results of the aforementioned study that recommend using it for treating OA Pain in cats.

GLUCOSAMINE AND CHONDROTINS

Very few studies with conflicting results in dogs. The data from the strongest studies did not find any positive results. The data for all is of low to moderate quality. An overall rating of the strength of the evidence concludes that one can have a low to moderate level of comfort with the results of the aforementioned study that recommend using it for treating OA in dogs.

One level –II study in cats found no positive clinical effects. No evidence to support the use in cats.

GREEN LIP MUSSEL POWDER – GLYCO-FLEX

Four level II - III studies, 3 show positive effects. Very small group sizes. The data for all is of low to moderate quality. An overall rating of the strength of the evidence concludes that one can have a low to moderate level of comfort with the results of the aforementioned study that recommend using it for treating OA pain in dogs.

No studies in cats.

AUTOLOGOUS STEM CELL (Not really Stem Cells)

In dogs, two level II and three level III studies. Some positive results. One (2014) study suggest effects < 3 months. Question if it should be used primarily or adjunctive are still unanswered. The data for all is of low to moderate quality. An overall rating of the strength of the evidence concludes that one can have a low to moderate level of comfort with the results of the aforementioned studies that recommend using it for treating OA pain in dogs.

No data in cats.

ALLOGENEIC STEM CELL

Very limited small studies available. Data is limited to support the use for OA Pain in dogs.

No data in cats

AUTOLOGOUS PROTEIN PRODUCTS (PRP, APS etc.)

Three studies' (2 level II and one level 3) results suggest some benefits. Not all the same product and so it is difficult to assess consistency of outcomes. The data for all is of low to moderate quality. An overall rating of the strength of the evidence concludes that one can have a low to moderate level of comfort with the results of the aforementioned studies to support the use for OA pain in dogs.

No data in cats

ANTI-NERVE GROWTH FACTOR ANTIBODY

One level I and one level II provide data showing decrease pain and improved function in dogs treated with canine NGF-antibody. The data for all is of moderate to high quality. An overall rating of the strength of the evidence concludes that one can have a moderate level of comfort with the results of the aforementioned study that support its use for OA pain in dogs.

Feline-specific monoclonal antibody for NGF: One level I study - showed 6-week duration of analgesic effect from a single injection in cats with pain associated with degenerative joint disease (OA). The data for all is of moderate quality. An overall rating of the strength of the evidence concludes that one can

have a moderate level of comfort with the results of the aforementioned study that recommend use for OA pain in cats.

Appendix 1: Strength of evidence ranking

A “high level of comfort” ranking advises that qualified scientists agree that a specific claim is scientifically valid. This highest level of ranking possesses a very low level of probability that new scientific data will overturn the conclusion that the relationship in question is valid or significant. This rank is based on relevant, high quality studies of study design Types I and II with sufficient numbers of individuals resulting in a high degree of confidence that the results are relevant to the target population.
A “moderate level of comfort” ranking describes a relationship as promising but not definitive. The claim is based on relevant, high to moderate quality studies of study design Type III and higher and sufficient numbers resulting in a moderate degree of confidence that the results could be extrapolated to the target population.
A “low level of comfort” ranking possesses a low consistency. The relationship is based on moderate to low quality studies of study design Type III and has insufficient numbers of individuals tested resulting in a low degree of confidence that the results could be extrapolated. Uncertainties would also exist as to whether the proposed benefit(s) would be physiologically meaningful and achievable.
An “extremely low level of comfort” ranking has very low consistency and is based on moderate to low quality studies of design Type III and insufficient numbers resulting in a very low degree of confidence that the results could be extrapolated.