Osteoarthritis in Dogs and Cats: Why is it so Important to Know What’s Going on in There?
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Osteoarthritis is the most common chronic musculoskeletal disease in dogs and cats. It is estimated approximately 60% of all dogs and close to 90% of aged adult cats are affected by this disease. Osteoarthritis (OA) is not a single disease entity but rather a disease process. It is a common final pathway for a failing synarthroidal or diarthroidal joint. It must be remembered the joint is an organ therefore OA affects not only cartilage but also involves the synovium, synovial fluid, ligament, fat and underlying bone. The condition may be confined to the joint but the entire patient is affected due to the pain and disability of OA. Patients with OA have decreased activity and performance, decreased ROM, muscle atrophy (often generalized sarcopenia), pain, decreased flexibility, loss of strength and increased joint stiffness.

OA in dogs is always a secondary problem caused either by abnormal stress on a normal joint (such as may happen with trauma) or normal forces on a joint that has an underlying abnormality (e.g., joint laxity, or instability from hip dysplasia, or cruciate disease). Either scenario will result in a gradual loss of articular cartilage (the morphological marker for OA) and joint impairment. OA in cats can be secondary to genetic disease or trauma but often no initiating cause can be identified.

Tissues in the synovial joint
To truly understand OA requires a working knowledge of the metabolism of the tissues of the synovial joint. It is important to remember that all the components of a joint adapt their composition and appearance to match functional demands. The demands are usually mechanical but can change with immobilization, injury, training or inactivity.

The tissues have a certain form and characteristic but change due to demands on the tissue. Stress and strain can change the type of collagen, and amounts, cross linking, PG types and architecture of the joint. Wolff’s law tells us about changes in bone due to demand—there are similar changes in tendons and ligaments.

What makes up a joint?
- Bone
- Articular Cartilage
- Synovium
- Tendon
- Ligament
- Menisci
- Labra
- Fat Pads
- Bursae
- Synovial Fluid

Most of these structures are made up of connective tissue. Connective tissues are made up of widely dispersed cells in a large volume of extracellular matrix (ECM). The function of the connective tissue is determined by its ECM not the cells in the tissue. Tendons and ligaments are considered dense connective tissues with tendons being more elastic than ligaments. Important cell types found in joints are fibroblasts in tendons, ligaments, menisci, and labra, chondroblasts in articular cartilage and osteoclasts and osteoblasts in bone.

Extracellular matrix
The ECM is mostly protein and water and has both interfibrillar (ground substance) and fibrillar components. The fibrillar component is composed of mostly collagen and elastin. Collagen is the most abundant protein in the body, has a tensile strength similar to steel, is responsible for the integrity of the tissues and their resistance to tensile force.

Interfibrillar component
This is mostly glycoproteins and proteoglycans (PGs).

PG characteristics
- Distinguished by protein core and attached glycosaminoglycans (GAGs)
- Attract water through attached GAGs
- Regulate collagen fibril size
- Attach to Hyaluronan to form large aggregates called aggrecans
• Are increased in tissues subjected to alternating cycles of compression.

**Glycosaminoglycans (GAGs) exist mostly in 2 classes**
- Glucosaminoglycans—Heparan sulfate and keratin sulfate—contain D-glucosamine
- Galactosaminoglycans—Chondroitin sulfate and dermatin sulfate—contain D-galactosamine.
- Exception is Hyaluronic acid (hyaluronan) which is non sulfated D-glucosamine and D-glucuronic acid and does not attach to a core protein. In synovial fluid, hyaluronan is produced by type B synoviocytes but in the ECM it is produced by chondrocytes. Synovial hyaluronan acts as a lubricant and molecular barrier.

PG aggregates (aggrecans) are a number of PGs linked together by link proteins and attached to Hyaluron. Along with collagen they are the major weight bearing macromolecule in the articular cartilage. During metabolism PGs are broken down by enzymes matrix metalloproteinases (MMPs) and aggrecanase. In acute inflammation MMPs increase in number and disrupt the balance of production and destruction in the joint.

**Etiology of osteoarthritis**
1. Genetic predisposition—Hip dysplasia, elbow dysplasia
2. Aging—Chondrocytes synthesize smaller aggrecans, less functional protein and there is an accumulation of advanced glycation end products in the Type II collagen network. Decreased amounts of chondroitin sulfate are produced and increased amounts of keratin sulfate are produced. Keratin sulfate has less ability to imbibe water and therefore cartilage is stiffer and less resistant to deformation.
3. Obesity—increased load on joint mechanically. Adipose tissues is pro-inflammatory and produces increased levels of tumor necrosis factor (TNF), IL-6 and leptin. Obesity causes osteoarthritis through action of adipokines.
4. Early neutering—this appears to be the case for some joints.
5. Exercise, diet, housing—Over exercising at a young age can damage joints. There are no studies validating home made diets vs commercial diets to prevent the development of arthritis.

**Pathogenesis of Osteoarthritis**
The formation of OA involves all the tissues of the synovial joint. Changes include alterations of the metabolism and morphology of the articular cartilage, and subchondral bone, osteophyte and enthesophyte formation and synovial inflammation and fibrosis. Changes also occur in the soft tissue structures and the ipsilateral musculature due to disuse and inhibition. Changes in the central nervous system occur due to chronic pain leading to pain sensitization.

A normal healthy cartilage looks like the figure below.

Orientation of the cells and relatively little PG in Zone 1, the Tangential Zone, allows the surface of the joint to withstand high tensile stresses resisting deformation and distributing the load across the joint. Loss of this layer as happens in early OA changes the biochemistry within the cartilage. Zone 2 and 3 contain more PG and this allows them to withstand more compressive loads. PGs have a high affinity for water and when the cartilage is loaded slowly this weeps out onto the articular surface to lubricate the joint. In areas of high stress the cartilage is stiffer. In areas of low stress the cartilage is softer. If excess force is put on softer cartilage, OA can result. The subchondral bone has a large area that meshes with the cancellous bone and is very deformable. This allows it to distribute the load. When OA occurs the subchondral bone becomes stiff. The most profound changes are in the major weight bearing areas.

**Three stages of OA**
**Stage one**
- Imbalance in the anabolic and catabolic processes in the the cartilage
- ECM degrades and water content increases
- Size of aggrecan molecules in matrix decreases
- Structure of collagen network is damaged which leads to increased stiffness of cartilage.
- Macrophages in the synovium produce TNF alpha, IL-1Beta, IL-17, IL-18—all pro inflammatory. These affect the chondrocytes and activate the MMPs and aggrecanase which break down the matrix.

**Stage two**
- Chondrocytes proliferate and increase metabolic activity—produce more MMPs to try repair damage—decreased TIMP. Chondrocytes express COX-2 and produce Prostaglandin E2. This enhances the degradation of aggrecan and Type II collagen
- Cell clusters form to try and repair damage but catabolism eventually takes over.

**Stage three**
- Repair can not keep up with damage and cartilage is lost. Chondrocytes produces nitric oxide (NO) synthase which cause progressive cartilage loss. NO inhibits matrix synthesis, activates MMPs and apoptosis.
Degradation of the ECM of the articular cartilage and cell death are key processes in osteoarthritis.

**Pain in OA**

Our understanding of joint pain is poor—much comes from human models.

Joint nerves are A beta, A Delta and C fibers. Only cartilage has no nerve endings so stimulation does not produce pain. Silent nociceptors only respond when there is inflammation in the joint.

Synovium—key tissue in the origin of pain of OA. Cytokines and growth factors are produced by the synovial lining cells and inflammatory mediators which sensitize the silent nociceptors. Synovial inflammation, once established, can alter the metabolism of resident synoviocytes, the major biosynthetic source of hyaluronan (HY) in synovial fluid. Inflammatory mediators released from local synovial cells and infiltrating leukocytes can promote increased vascular permeability and the accumulation of plasma in synovial fluid, thereby decreasing HY concentration. This dilution of HY and reduction in its molecular weight due to abnormal synthesis by synoviocytes results in a decrease in the viscoelasticity of synovial fluid and thus its ability to lubricate and protect articular cartilage. This sets up a vicious cycle of cartilage degradation and pain.

Joint pain results in central sensitization which causes increased pain. COX enzymes play a role in central sensitization and COX inhibitors such as NSAIDs prevent establishment of central sensitization. Central sensitization can increase joint pathology while suppressing it can decrease joint pathology.

** A direct effect of NSAIDs at the level of the joint can result in a reduction in disease progression..NO induces cell death. NO is produced by chondrocytes when they are stimulated by pro inflammatory cytokines. COX-2 inhibitors block this by blocking the pro inflammatory cytokines. NSAIDs are still the most important treatment in OA***

**References**
Managing the Pain of Osteoarthritis in Dogs and Cats
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Osteoarthritis (OA) is one of the most common chronic musculoskeletal diseases and causes of lameness in the dogs. The osteoarthritic disease process involves the entire synovial joint, encompassing the synovium, cartilage and underlying bone. Joint failure results from an abnormal mechanical strain causing damage to normal tissue or failure of pathologically impaired articular cartilage and bone under the influence of normal physiological strain or a combination of both. In both cases, the end point is cartilage loss and joint impairment. Osteoarthritic chondrocytes show an altered phenotype characterized by an excess production of catabolic factors, including metalloproteinases and reactive oxygen species (NO). These factors constitute potential therapeutic targets and some new drugs and nutraceuticals have been proposed to promote the return to homeostasis.

It is important to remember that the pain of OA is not felt in the articular surfaces, instead the peri-articular structures such as the inflamed synovium, fibrotic joint capsule, or weak tendons, ligaments or muscle. OA is a disease of the entire joint involving synovitis, atrophy and fibrosis causing pain and progressive degenerative disease.

In recent years the human literature has identified OA pain as maladaptive pain that resembles true neuropathic pain. Maladaptive pain is pain as a disease and involves the creation of peripheral and/or central sensitization.

Pharmacological pain relief

The first line drugs for treatment of osteoarthritis are the Non Steroidal Anti-Inflammatory Drugs (NSAIDs). A number of NSAIDs have been approved for use in dogs and fewer in cats. Generally NSAIDs inhibit one or more steps in the metabolism of arachidonic acid. This class of drugs ameliorates the symptoms of osteoarthritis but also has a role in preventing central sensitization through COX inhibition.

Actions of NSAIDs
Stresses on the joint lead to production of inflammatory cytokines released by synovial cells, chondrocytes, macrophages and fibroblasts. These proinflammatory cytokines, including certain interleukins and TNF-alpha, lead to upregulation of COX-2 enzymes and production of eicosanoids such as PGE2, and the upregulation of matrix metalloproteinases. Normally during metabolism PGs are broken down by enzymes matrix metalloproteinases (MMPs) and aggrecanase. In acute inflammation MMPs increase in number and disrupt the balance of production and destruction in the joint. There is shift toward breakdown of articular cartilage resulting from an imbalance between MMPs and their TIMP inhibitors, leading to thinning and destruction of the cartilage tissue and perpetuation of the inflammatory cascade with PGE2 production and subsequent pain.

NSAIDs block PG synthesis by binding to and inhibiting COX. The major therapeutic and toxic effects of NSAIDs result from this action. The major "safe" NSAIDs are said to be COX2 selective although these do have some COX1 effects.

Adverse events

Adverse side effects of NSAIDs can include gastric upset, vomiting, diarrhea, inappetence, gastric bleeding, platelet inhibition, analgesic nephropathy, liver and cardiac problems. Inappetence is the most common side effect in cats.

Most adverse events occur within 2 to 4 weeks of commencement of the NSAID and stop soon after drug is discontinued. NSAIDs can cause gastric erosions but unlikely that these would occur without clinical signs. Perforations are most likely caused by concurrent use of steroids and NSAIDs or by using high doses of NSAIDs.

Nephrotoxicity can be seen in patients with pre-existing renal disease, hypotension, hypovolemia, congestive heart failure or diuretic administration. Hepatic necrosis appears to be due to an inherited sensitivity to the molecule used and not a true toxicosis.

Common NSAIDs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade name</th>
<th>Dose</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carprofen</td>
<td>Rimadyl—Zoetis</td>
<td>4.4mg/kg q 24 hours or 2.2mg/kg q 12 hours</td>
<td>Dogs only</td>
</tr>
<tr>
<td>Deracoxib</td>
<td>Deramaxx- Elanco</td>
<td>1-2 mg/kg q 24 hours</td>
<td>Dogs only</td>
</tr>
<tr>
<td>Firocoxib</td>
<td>Previcox—Merial</td>
<td>5 mg/kg q 24 hours</td>
<td>Dogs only</td>
</tr>
</tbody>
</table>
Long term use and safety in OA patients

- Use a veterinary approved drug at label dose—can be used long term and may show improvement in disease from 6 months to 1 year
- Meloxicam and Robenacoxib are metabolized in cats by oxidation not glucuronidation. Long term oral use has been safely demonstrated.
- No one veterinary approved NSAID has been proven to be safer than another.
- Veterinary approved products are safer than non veterinary approved products.

Nutraceuticals that work as well as drugs (and are proven winners)

Omega 3 fatty acids

There are a number of Randomized Controlled Clinical Trials (RCCT) proving the efficacy of Omega 3 fatty acids—fish oil or Marine Oil (Algael Oil) but not flaxseed oil.

Arachidonic acid is the primary substrate for the lipoxygenase (LOX) and cyclooxygenase (COX) enzymes. This fatty acid is derived dietary sources and stored in phospholipids of the cell membrane until needed. AA is a member of the omega-6 fatty acid family. AA can be partly replaced in cell membranes by the omega-3 fatty acid EICOSAPENTANOIC acid (EPA). EPA can be used by the LOX and COX enzymes to produce eicosanoids. When EPA is used by the COX and LOX enzymes, they produce the eicosanoids PGE3, thromboxane (TX) A3 and LTB5, which are less active and relatively anti-inflammatory compared to their counterparts produced from AA.

Omega 3 Fatty Acids can be supplied by supplemented diets (Hill's J/D, Purina JM and RC Mobility Support) or directly supplemented from fish oil capsules or liquid. Dose for supplementation varies but most accepted is:

Injectables

Polysulfated glycosaminoglycans

Adequan (PSGAG) and Cartrophen (Sodium pentosan polysulfate) are the 2 products that are available.

Polysulfated glycosaminoglycans (PSGAGs) are a semisynthetic product (derived from bovine trachea) structurally similar to the GAGs found in articular hyaline cartilage. PSGAGs stimulate collagen synthesis and inhibit collagen breakdown as well as decrease pain and inflammation. Several studies have documented positive effects when administering PSGAGs (Adequan) to dogs with hip dysplasia and osteoarthritis. One study found decreased hip laxity in dogs treated with Adequan twice weekly from 6 weeks to 8 months of age compared to age-matched controls. It is recommended to begin treatment as early in the disease process as possible in order to slow the progression of cartilage damage. The strength of evidence for PSGAGs used at the labeled dose is considered high.

Dose: 5mg/kg once weekly x 4 to 6 weeks then once monthly in dogs, cats first 4 weeks is the same but 2nd month every other week then once monthly

Cartrophen

Pentosan polysulphate—this product is used in Canada, Europe and Australia. Similar actions to Adequate. Dose is 1ml/33kg once weekly for 4 weeks then once monthly.

Other drugs for chronic/maladaptive pain

Tramadol

In humans tramadol is known to exert its pain modifying effect through two metabolites; one enhances inhibitory neurotransmitters (serotonin, norepinephrine), and the other (0-desmethytramadol, or "M1") metabolite is a weak opioid (1/100th the mu-receptor affinity of morphine.) Tramadol has a very short half-life (1.7 hours) in the dog, and it appears that dogs produce very little of the M1 opioid metabolite. Evidence for a pain-modifying effect of oral tramadol remains unknown at this time. Plasma levels in dogs are much lower following oral administration than in humans. One study of oral tramadol reports a statistically significant increase of mechanical threshold levels, but only at the 5- and 6-hour time point. One study does find oral tramadol effective as part of a multimodal analgesic protocol to control cancer pain, but others have found it (not unsurprisingly) inferior as a solo agent to multi-modal pain management.
Gabapentin
Gabapentin is said to be effective in neuropathic pain states such as post-herpetic neuralgia (shingles) in people. Gabapentin binds to the alpha 2 delta subunit of the voltage-gated calcium channel resulting in the decreased release of excitatory neurotransmitters such as glutamate. It also increases brain concentrations of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter. It has also been used in people for fibromyalgia and diabetic neuropathy pain, and restless leg syndrome, and in acute pain states it may reduce the opioid need of some patients.

Gabapentin is used in dogs with neuropathic pain or in dogs who pheotypically appear as if they have neuropathic pain i.e. osteoarthritis. Dosage of this drug is usually 10 mg / kg BI but geriatric dogs may need a decreased dose of 5,g /kg.

Amantadine
Amantadine is an antiviral drug but it also increases concentrations of dopamine in the CNS as well as being an antagonist at the NMDA receptor. It affects central pain sensitization via NMDA receptor and appears to enhance the analgesic effects produce by opioids, NSAIDs and gabapentin. In dogs, one clinical study using 3 to 5 mg/kg once daily in combination with meloxicam showed significant improvement using client-specific outcome measures for activity on day 42 of administration but not on day 7 or 21. This may be a function of dosage frequency as pharmacological data indicate twice daily dosing is more appropriate.

In cats, there is very good oral bioavailability but a short half suggests twice daily dosing in the similar range to dogs. Central sensitization must be present for efficacy to be demonstrated.

Dosage is usually 10 mg .KG BID or in cats 3 to 5 mg /Kg BID to start

Amitriptylline
Amitriptyline and other TCAs are commonly used in neuropathic pain in people. They produce serotonin and norepinephrine reuptake inhibition, some NMDA antagonism, sodium channel blockade and are anti-inflammatory. In the dog suggested dosage is 3-5 mg/kg every 12 hours.

Acetaminophen
Contraindicated in cats! It has been used in dogs for a washout period if switching NSAIDs and may be combined with codeine or tramadol. May be beneficial for dogs with renal dysfunction but should not be used immediately postoperative. Even at recommended doses there is some potential for toxicity. Dose: 10 – 15 mg/kg PO q8h; if using long-term (>5 days) consider giving q12h at the lower end of dosing range.

Oral opioids
Maladaptive pain secondary to peripheral nerve damage shows decreased sensitivity to opioids. Oral opioids have a very low bioavailability due to metabolism in the liver. Codeine has the highest bioavailability and is often combined with acetaminophen in dogs only.

Dose: 1-2 mg/kg q 4 hours
If combined with acetaminophen dose on the acetaminophen fraction and do not exceed 2mg/kg of codeine.

Cortisone
Corticosteroids are usually the last drug used and are not analgesic but do reduce inflammation. Intra articular injections are common in humans and becoming more common in dogs. Intra articular steroids have been shown to protect articular cartilage in experimental canine OA; however, repeated use may also have deleterious effects on joint tissue from suppression of cartilage matrix synthesis. Benefits usually outweigh risks. Strict aseptic techniques are needed for these injections.

On the horizon
A new EP4 receptor blocking drug, grapiprant, will soon be coming to market. It is rumoured to replace NSAIDs in dogs and will have applications in cats as well. The company producing this drug is Aratana. It should be to market in 2016.

References
Nonpharmaceutical Treatment of Osteoarthritis: Rehabilitation, Acupuncture, and More
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For many years OA was managed with a single pharmaceutical agent if and when the clinician determined the animal was suffering. Recently it has been realized that pain is a very complex process and involves signalling molecules, pathways, substances, receptors and transmitters with different modes of action. It is unrealistic to think only one pharmaceutical could be effective in eliminating chronic pain. It is equally unrealistic to think that drugs alone can manage OA effectively for the life of the animal. A multimodal approach to the treatment of OA is necessary and the best approach.

Weight loss and diet
Prevalence of OA is likely close to 60 % of all dogs and over 50 % of all dogs are overweight. Excess weight causes an excess load on an abnormal joint, creating more pain. In addition the adipose tissue secretes adipokines which are pro-inflammatory and these increase the overall inflammation in the joints and elsewhere in the body.

Purina Longevity study determined that dogs who are normal weight live on average 2 years longer than their obese siblings. Musculoskeletal problems, especially OA were the leading cause of death or euthanasia and doubled the need for pain medications.

To have success with weight loss, you need to be able to calculate the Resting Energy Requirement ( RER) and determine calories needed for weight loss. Generally for weight loss the pet needs 60 to 80 % of RER. A weight loss diet that is higher in protein (minimum 1 g/lb of body weight) tends to maintain lean body mass. Just having the client cut down the number of calories with their existing diet can promote muscle loss instead of fat loss, so true weight reduction diets are needed. Here is an example of how to calculate amount of food needed.

Determine RER from Body Condition Score on a 9 scale. For every point that the dog or cat is overweight over the ideal 5/9 body condition score, the pet is 10 % obese. For example a 10 kg cat with a body condition score of 7/9 is 2 x 10% or 20% over ideal weight. To determine Lean body weight in kilograms 10/1.20 = 8.3kg. Take this lean body mass of 8.3 and raise it to the 0.75 power. Multiply this result by 70 to give the RER. In this case a cat with a lean body mass of 8.3 kg has a RER of 342 kcal. Multiply this by 0.8 = 272 kcal. This is the number needed for weight loss. Had the example been for a dog I would have used 7. Use this formula and this calculation rather than amount on bag or can for weight loss. If supplementing with Omega 3 fatty acids be sure to take those calories into account. Consider using 1/2 joint diet and 1/2 weight loss diet and then adding additional Omega 3s for cats or using one of the new combination weight loss and joint health diets (Hill’s).

Environmental modification and assistive devices
Simple environmental modifications can have a positive effect on old painful patients. Raising food and water dishes, putting down area rugs or carpet to reduce slipping, installing ramps and using baby gates to limit dangerous areas are all good ideas for household modifications. A foam bed or other soft area to lie on can cushion old joints. Harnesses, slings, booties, power socks, braces and orthotics are all examples of assistive devices that can be used. Sometimes carts and wheel chairs are also necessary.

Acupuncture
Acupuncture can be used to relieve pain, cause an autonomic nerve response, increase the rate of nerve regeneration, and cause surgical analgesia. Studies have found that acupuncture and non-acupuncture points were differentiated by their connection to different pathways in the central nervous system. They found that the pathway connected to the acupuncture point is different from the pathway connected to the non-acupuncture point. In addition, the pathway connected to the non-acupuncture point is inhibited within the lateral periaqueductal gray when the analgesia inhibitory system (AIS) is activated. They also found that analgesia caused by stimulation of the acupuncture point is naloxone reversible, while that caused by stimulation of the non-acupuncture point after a lesion in the AIS is dexamethasone reversible. Stress-induced analgesia caused by low frequency electrical shock was naloxone as well as dexamethasone reversible.

There are multiple theories as to how acupuncture works in humans and animals alike. It is important to understand that no one theory explains all the different effects of acupuncture. Just as research is continuously being done to further develop western medicine, additional research is being done with both human and animal acupuncture to further our understanding of this ancient healing art. The most current theories are: 1) The Gate Theory; 2) Endogenous Opioid Theory; 3) Autonomic Nervous System Input Theory; 4) Humoral Theory; 5) Bioelectric Theory; and 6) Traditional Oriental Medicine Theory.

1. The gate theory
A beta sensory neurons close the gate to larger pain fiber sensations.

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2. Endogenous opioid theory
Studies have found that acupuncture analgesia could be reversed by naloxone. It was also determined that a cross-tolerance can develop between acupuncture and morphine. Levels of the opiate peptide NAGA and beta-endorphins were shown to increase in the brain and cerebrospinal fluid (CSF) after acupuncture. It has also been shown that levels of met- and leu-enkephalins significantly increase in the brain after electrical acupuncture. Opiates are also known to have systemic effects that can be produced by acupuncture. For example, opiate receptors in the gut are responsible for decreasing peristalsis and increasing segmental contractions, thus effectively controlling diarrhea.

3. Autonomic nervous system input theory
Type A-delta visceral and somatic fibers have a similar distribution in the dorsal gray matter and tract of Lissauer. Inputs from both converge in the spinothalamic tract. Visceral A-delta fibers form reflex arcs with propriospinal afferents, and can cause muscle cramping secondary to visceral inflammation. Conditions of somatic pain can also cause visceral manifestations of disease. These interactions account for the phenomenon of “referred pain.” Stimulation of acupuncture points can cause a reflex arc, resulting in sympathetically induced segmental superficial and visceral vasodilation. This explains how acupuncture can be effective in the treatment of internal organ dysfunction.

4. Humoral theory
This theory was first postulated after studies showed that a transfer of blood, CSF, or brain tissue from an animal under acupuncture analgesia to an animal not receiving acupuncture resulted in analgesia of the recipient. This analgesia was generalized and reversed by naloxone. The analgesia level required for surgery took twenty to thirty minutes of stimulation to reach its peak and lasted hours after stimulation of the points had ceased. Acupuncture has also been shown to cause systemic increases in growth hormone, prolactin, oxytocin, luteinizing hormone, white blood cells, immunoglobulins, antibodies, and interferons depending on which points are stimulated (66).

5. Bio-electric theory
Becker and Reichmanis (3), in 1976, proposed a theory that the healing and analgesic properties of acupuncture are based on a DC current system. In this system, electric signals are generated and propagated by Schwann cells, satellite cells, and glial cells. Acupuncture points, like amplifiers, would boost the DC signal along the nerve pathways. Insertion of a metal acupuncture needle would, in effect, short-circuit the system and block pain perception.

6. TCM theory
According to TCM theory, Qi, also known as Chi, energy, or life force, circulates through each of the meridians or channels every twenty-four hours. Each channel is connected energetically to a TCM organ. The channels derive their names from the organ upon which they have the greatest influence. A blockage of Qi circulation manifests as dysfunction or disease. By stimulating or sedating energy levels at acupuncture points, the body is brought into balance and healing is facilitated.

Physical rehabilitation
The goals of rehabilitation include the restoration, maintenance and promotion of optimal function and quality of life as they relate to movement disorders. The majority of rehabilitation therapeutics involves manual therapies including joint mobilizations, and therapeutic exercises. Equipment used on a regular basis in veterinary rehabilitation includes physioballs, therapy bands, rocker/wobble boards, cavaletti poles and land treadmills. Hydrotherapy equipment can include pools, resistance pools and underwater treadmills. Modalities such as hot and cold therapy, laser, electrical stimulation, shock wave therapy and therapeutic ultrasound can also be used. Regenerative medicine with platelet rich plasma and stem cells is now also a part of rehabilitation and pain management.

Manual therapies
Joint mobilizations—a manual technique used to assess a joint and improve its movement (arthrokinematics). Joint mobilizations improve joint lubrication, modulate mechanoreceptors, and decrease sensory input thus relieving pain. Therapeutic glides are ranked Grade I to V using the Maitland Mobilization Scale.

Massage is soft tissue massage and soft tissue mobilization. Massage can decrease excessive tissue tension by aiding in removal of chemical substances in soft tissue that activate chemical nociceptors. Soft tissue massage can also, by the Gate Theory, reduce pain by stimulating large rapidly conduction fibers, selectively closing the gate against smaller pain fiber input.

Thermal therapy
The effects of thermotherapy are vasodilation with secondary increased local circulation, decreased pain, relaxed muscle tone, reduced muscle spasm, increased tissue extensibility, increased cellular metabolism, and increased local tissue oxygenation. Heat is generally used to reduce pain from arthritis, trigger points and muscle spasms, and to prepare tissues for exercise or stretching. Precautions of using heat therapy include impaired thermal sensation, recent hemorrhage, malignancy, and acute inflammation. Heat can be applied by gel packs, hot towels, or therapeutic ultrasound.
Cryotherapy can be applied via ice bath, ice massage, ice pack, vapocoolant gel, or circulating ice compression units. The beneficial effects of cryotherapy include vasoconstriction; reduced cellular metabolism; decreased nerve conduction velocity, and decreased production of pain mediators, leading to analgesia; reduction of edema and decreased muscle spasm. Metabolism may be decreased by more than 50%, which facilitates oxygen diffusion into the injured tissues. Joint range of motion is improved through suppression of excitatory muscle spindle afferents. Intermittent pneumatic compression, when combined with cryotherapy has been shown to prevent edema formation, increasing blood flow, and stimulation of tissue healing. Although static compression is effective in edema reduction, intermittent compression optimizes lymphatic drainage. Game ready is commonly used for pain reduction post surgery.

Laser

LASER™ is Light Amplification by Stimulated Emission of Radiation. By definition, a laser must be collimated and monochromatic. Penetration of laser energy is determined by the wavelength, and many wavelengths are patented. The physiological effects of laser stimulation include accelerated cell division via mitochondrial stimulation, increased leukocyte phagocytosis, stimulation of fibroblast production, enhanced synthesis of ATP, and angiogenesis. Treatment with laser is indicated for pain management, control of inflammation, and tissue healing.

Electrical therapy

Electrical stimulation (ES) can affect the sensory and the motor nerves. Indications for ES include wound healing, pain control/relief, reduction of inflammation, muscle re-education, reversal of atrophy, and strengthening. Electotherapy works at the cellular level to cause excitation of nerve cells, changes in cell membrane permeability, and stimulation of protein synthesis, osteosynthesis and fibroblast formation. On the tissue level, electotherapy causes skeletal muscle and smooth muscle contraction. On the segmental level, electotherapy facilitates muscle-pumping action, which improves joint mobility and circulatory and lymphatic drainage. ES can be TENS or NMES.

Sound therapy

ESWT has been applied to painful OA lesions in veterinary practice, including hip and elbow dysplasia and Supraspinatus tendinopathy with excellent pain relief results being reported. ESWT works by releasing a sudden high-powered shock wave resulting in tissue modulation in a very focused depth of tissue. This modality does require deep sedation or anesthesia as the treatment is uncomfortable for the patient, however the patient experiences pain relief immediately post treatment, which can last for days to weeks. The mechanism behind the pain-relieving function of ESWT is thought to be due to increased serotonin activity in the dorsal horn, and descending inhibition of pain signals.

Therapeutic exercises

Therapeutic exercise contributes to pain management in through Exercise Induced Hypoalgesia (EIH) which results from activation of the opioid system with beta-endorphin release from the pituitary. It is also believed that exercise can activate large afferents and that mechanical hypoalgesia is induced by repeated low load exercises regardless of exercise mode.

Exercises are used for stretching, strengthening, balance, proprioception, flexibility, endurance and muscle re-education

Exercises for stretching, front and hind limb and balance and proprioception

- PROM, High 5s, Ball Work, Wheelbarrow, Step ups, Sit to Stand, Backwards Walking, Side stepping, Rhythmic Stabilization, Cross legged standing, Crawling, Sit to Be

Regenerative medicine

Stem cell and PRP (Platelet Rich Plasma) can be used for pain management. Progenitor cells present in almost every tissue that are self-renewing, able to become different tissue types and signal other cells to come in and repair tissue. Adipose derived and bone marrow derived mesenchymal stem cells are used. Benefits are more like due to growth factors. PRP contains growth factors as well. This is a wide topic and only gets a brief mention here.

References

What exists for painful veterinary patients beyond rest and NSAIDs? What can I do for those really painful patients? Where can I find help and answers for my pain questions? What are the standards of care for pain? Are there any non pharmalogical modalities that really work for pain?

These are all very common questions for veterinary practitioners to ask in this changing world. We will deal with what’s new and what is on the horizon for pain in veterinary practice.

Standards of care for pain in dogs and cats is now outlined in the new AAHA/AAFP pain guidelines. Here is an excerpt summarizing the guidelines:

The 2015 guidelines summarize and offer a discriminating review of much of this new knowledge. Pain management is central to veterinary practice, alleviating pain, improving patient outcomes, and enhancing both quality of life and the veterinarian-client-patient relationship. The management of pain requires a continuum of care that includes anticipation, early intervention, and evaluation of response on an individual-patient basis. The guidelines include both pharmacologic and nonpharmacologic modalities to manage pain; they are evidence-based insofar as possible and otherwise represent a consensus of expert opinion. Behavioral changes are currently the principal indicator of pain and its course of improvement or progression, and the basis for recently validated pain scores. A team-oriented approach, including the owner, is essential for maximizing the recognition, prevention, and treatment of pain in animals. Postsurgical pain is eminently predictable but a strong body of evidence exists supporting strategies to mitigate adaptive as well as maladaptive forms. Degenerative joint disease is one of the most significant and under-diagnosed diseases of cats and dogs. Degenerative joint disease is ubiquitous, found in pets of all ages, and inevitably progresses over time; evidence based strategies for management are established in dogs, and emerging in cats. These guidelines support veterinarians in incorporating pain management into practice, improving patient care.

**Pain scoring is important and veterinarians need to use pain scales**

Although the Glasgow Composite Pain Scale is the only validated Acute pain scale, the Colorado State Acute Pain scales for post surgical pain are easier to use. They rely on pictures and should be scored by the same person as the inter rater scores could vary.

Chronic pain scales include the Helsinki Chronic Pain Scale, the Canine Brief Pain Inventory, the Cincinnati Orthopaedic Disability Index and others. The important thing is to familiarize yourself with one of these scales and use it consistently.

**New or new to you techniques to consider**

Local anesthetics with every surgery—Line blocks, Ring blocks, testicular and ovarian blocks.

For chronic orthopedic disability regional anesthesia with bupivicaine can be used to relieve pain so muscles can be strengthened—consider blocking femoral or sciatic nerves—may need to use a nerve finder to do this.

Epidurals—not really new for orthopaedic surgery but consider these for blocked cats ( sacral epidural). For dogs with painful lumbosacral disease consider epidurals with methylprednisolone—it will not improve neurological function but will relieve pain.

- Ketamine—Subanesthetic doses as CRIs for painful surgeries—things that are likely to trigger maladaptive pain syndrome.
- Use of Amitriptyline for Chronic pain—much lower doses than needed for anxiety.
- Joint injections with HA and corticosteroids

**New information**

- Pruritis receptors are a subset of nociceptors that also respond to pain.
- Substance P and Glutamate can cause pain and itch.
- Itch can be inhibited by pain--mild scratching inhibits itch. In order to inhibit the itch signalling pathway you need to have both itch and pain as these overlap, so consider this when dealing with chronically itchy animals—this may be why amitriptyline works for pain.

**Glial cell dysregulation**

Originally thought that non neuronal cells (glia) had no input into the nervous system. However research has shown that microglia and astrocytes have an effect on the nervous system and how it handles opiates. Glial cells are key in the development of pathologic pain.

In every clinically relevant model of enhanced pain, the glial cells are activated, so if you block the glia cells you block pain. Glial cells monitor the CNS—they are very active cells—when they find danger they actively attack it--they release all kinds of substances.

The important thing to know is they amplify the pain transmission to brain, they up regulate the NMDA receptor numbers and down regulate GABA and glia glutamate transporters.
Glial cells enhance pain and PREVENT opiates from working.

What activates glia cells?—lots of stuff—Opioids, endogenous danger signals (leakage of blood—anything that should not be in the nervous system that causes cell stress and damage).

Most common endogenous danger signals are peripheral nerve injury, overuse of medication, diabetic neuropathy, spinal cord injury, bone cancer, arthritis, and pancreatitis. These conditions cause pro-inflammatory cytokines to be released.

Opioids activate the glial cells so this can actually block the pain control from the glial cells—if you block the spinal IL-1 the analgesia comes back. Opioid effects are different on neurons vs glial cells. The glial cell receptor is TLR4 (not me not right no ok receptor)—it is a major player in identifying endogenous danger signal and recognizes all lipids. Glial TLR4 is a driver of neuropathic pain. If the glial cells are blocked by + naloxone then it might be a stand alone treatment for neuropathic pain. Other cells involved are in blood vessels and these produce IL-1 (pro-inflammatory cytokines) and these can be blocked by naloxone.

When glial cells are active and you give opioid for pain it makes pain worse because the glial cells are induced to produce more IL 1 and block the opioid receptors. Primed state can occur for a period of time after prior activation—the glial cells are not activated they are waiting and the reaction comes back with a vengeance. Primed glial cells can be activated by aging, opioids, stress, trauma and inflammation.

Clinical relevance—prior surgery changes pain to chronic pain—this can be prevented by glial activation inhibitor.

Another interesting point—morphine can worsen post surgical pain. This is mediated by TLR4—so to control this you need to give a TLR4 blocker when you give morphine.

IL-10—anti-inflammatory interleukin—this is being developed for inter thecal injection.

Grapiprant—EP4 blocker that works in inflammatory cascade with no NSAID side effects.

Theracurmin—biologically active curcumin—water soluble.

**Non pharmacological**

- Acupuncture—more common and more accepted.
- PT modalities easily added to general practice—Laser, exercise therapy, hot and cold therapy, TENS
- Myofascial pain—this is something new to veterinary medicine. It is a myalgic condition in which muscle and tendon are the primary cause of pain. The syndrome is centered around the myofascial trigger point (MTrP). A myofascial trigger point is an extended contraction of a few muscle fibers that results in a painful knot. Dry needling is what is done to eliminate them. If you are interested there is an entire lecture on this topic.
- Regenerative Medicine—PRP and Stem cell
Pain is a multidimensional sensory experience that is intrinsically unpleasant and associated with hurting and soreness. It may vary in intensity (mild, moderate, or severe), quality (sharp, burning, or dull), duration (transient, intermittent, or persistent), and referral (superficial or deep, localized or diffuse).

Pain is divided into 2 categories: Adaptive and Maladaptive Pain. Adaptive pain is that which serves a purpose—to protect the body from harmful substances or protect the body while healing occurs. Adaptive pain can be either nociceptive or inflammatory. Nociceptive pain is pain that is transient from noxious stimuli. Inflammatory pain is spontaneous in response to tissue inflammation or injury. Both of these could be considered acute pain and will occur naturally post injury or inflammation and are limited in their scope and time frame. These types of pain are pain with a purpose—to protect and allow rest for healing.

Maladaptive pain is pain as a disease and it serves no useful purpose. Such pain may occur in response to damage to the nervous system (neuropathic pain) or result from abnormal operation of the nervous system (functional pain). Maladaptive pain is the expression of abnormal sensory processing and usually is persistent or recurrent. Maladaptive pain can result from peripheral or central sensitization. In peripheral sensitization inflammation and tissue damage produce a variety of nociceptor-sensitizing substances, including prostaglandins, histamine, serotonin, bradykinin, proteases, cytokines (tumor necrosis factor α), and nerve growth factor. This "sensitizing soup" lowers the nociceptor threshold to painful stimuli and activates "silent" or "sleeping" nociceptors, resulting in hyperalgesia (exaggerated response to noxious stimuli) and allodynia (painful response to normal stimuli).

Central sensitization occurs when severe (high-intensity) or chronic painful stimuli activate C fibers, causing the release of glutamate, substance P (Sub P), and brain-derived neurotrophic factor (BDNF) at central nerve terminals; this results in the activation of number of receptors producing acute and long-lasting dull, aching, burning pain sensations. Collectively, the activation of these receptors increases the activity of a host of signaling molecules that alter gene expression and change the responsiveness (sensitize) of the central nervous system to subsequent input. Chronic painful stimulation may result in neurochemical changes (neuroplasticity) in the spinal cord such that all stimuli produce pain. (Gaynor 37)

Pain assessment in cats
Currently the only validated acute pain scale for cats is the UNESP-Botucatu Multidimensional Composite Pain Scale. A shorter and easier to use pain scale is the Colorado State University Feline Acute Pain Scale. It involves a simple numeric scale with pictures outlining behavioural and psychological indicators of pain and includes response to palpation. This scale is not currently validated.

For chronic pain, specifically related to degenerative joint disease (DJD) in cats, the only validated system is the NCSU Comparative Pain Research Lab’s Feline Musculoskeletal Pain Index. Behaviors evaluated include litterbox use, grooming, fluidity of gait, temperament, appetite, allowing petting and general activity. Use of activity monitors is another possibility to determine a cat’s pain. These have been used in scientific research and will have a place in feline pain determination in the future.

No matter which system is used, results are best if the same person scores the cat’s pain each time to minimize inter rater variability.

Pain management in cats

Nonsteroidal anti-inflammatory drugs
NSAIDs are one of the most common drug classes used to treat pain, and there is a robust body of information indicating that NSAIDs are effective in treating acute pain in cats. They have antipyretic, analgesic, and anti-inflammatory properties, which make them appealing therapeutic options; however, remember that there is not, and never will be, a completely safe NSAID for use in cats. (Lascelles)

NSAIDs work to block the cyclooxygenase (COX) enzyme pathway to prevent production of eicosanoids and also work to inhibit central perception of pain. Eicosanoids are metabolically active compounds derived from 20-carbon fatty acids, usually arachidonic acid. The lipooxygenase (5-LOX) and cyclooxygenase (COX) enzymes are the rate-limiting steps in the production of leukotriene B4, thromboxane A2 and prostaglandin E2.

The ideal NSAID should:
- Spare COX-1 as much as possible (to prevent GI erosion and renal tubular necrosis)
- Inhibit COX-2 sufficiently for efficacy against pain and inflammation
- Spare enough COX-2 to allow it to function in normal everyday processes
Robenacoxib (Onsior - Elanco)
Robenacoxib is a targeted tissue selective and a unique COX-2 selective NSAID. It has a very short half-life (3 hours) in the blood, yet persists, and is active, for at least 24 hours in inflamed tissue in cats which demonstrates “tissue selectivity.” It is available in injectable and tablet form. Dosage: 1 mg/kg q 24 hours

Meloxicam (Metacam—Boehringer Ingleheim)
Meloxicam is an example of a preferential COX-2 inhibitor that has greater inhibition of COX-2 than COX-1. It is also tissue selective but has a longer tissue half-life than robenacoxib.

Used for years in Canada, Europe and Japan. Has a black box label in the US because labelled dose is 0.3 mg/kg once post surgery—too high a dose.

Canada has a specific Metacam for Cats with a reduced dose—this dose seems to be the safest. Dose is Injectable 0.1 mg/kg—one post surgery followed by oral dose of 0.05 mg/kg q 24 hrs for 5 to 11 days. Dose may be further reduced for long term therapy—we find 0.02 mg/kg once daily as a good oral dose for cats with chronic pain—this is study supported although the study was not blinded.

Opiates
Buprenorphine
A partial mu-agonist that is used to manage chronic pain in cats and is classified by the Drug Enforcement Administration (DEA) as a Schedule III controlled substance. Buprenorphine is not approved by the Food & Drug Administration (FDA) for use in cats. The drug may be administered SC, IM, IV, or buccally; buccal administration is the preferred route for chronic pain management. Dosage: 0.01–0.02 mg/kg SC, IM, IV, or transmucosal.

In July 2014, a new veterinary formulation of buprenorphine was FDA-approved and introduced into the marketplace (Simbadol, Abbott). At 1.8 mg/mL it is 6X more concentrated than the human commercial product Buprenex (0.3 mg/mL). It is labeled for postsurgical pain in cats, with a 24-hour duration with one injection at 0.24 mcg/kg subcutaneously (SC); it can be given daily for up to 3 days. The labeled dose is 0.24 mg/kg, approximately 10X the dose previously recommended. Shelf life 21 months unopened and 28 days opened.

Tramadol—can be used but not approved, variable results in dogs but cats do make the M1 metabolite so better results in cats. In cats it is a mu agonist and serotonin—norepinephrine reuptake inhibitor. Cats are sensitive to the side effects of this drug and the bitter taste makes it difficult for cats to accept.

Dose: 1-4 mg/kg q 8 to 12 hours

Fentanyl—patch forms—variable efficacy

Analgesic adjuvants
These are used in combination with NSAIDs or Opiates to treat chronic pain

Amantadine
Amantadine is an antiviral compound used in humans that is reported to exert an analgesic effect through NMDA receptor antagonism. Toxicity and kinetic studies have not been performed in cats. It is often effective however but can cause diarrhea in cats. Caution in cats with liver and kidney disease or seizures. Dosage: 3-5 mg/kg q 24 hours

Gabapentin
Gabapentin is an anticonvulsant that is used in cats for chronic pain particularly neuropathic pain. It is often used with amantadine and NSAIDs. It has been used to treat allodynia and hyperesthesia. Caution in cats with kidney disease—can be used at a reduced dose.

Dosage: 5 to 10 mg/kg q 12 hours

Amitriptyline
Amitriptyline, a tricyclic antidepressant, is usually administered in combination with an NSAID for feline chronic pain of neuropathic origin. Avoid in seizing animals or with liver disorders. Do not give along with Tramadol as you may cause serotonin syndrome.

Dosage: 1-2 mg/kg q 12 to 24 hours

Nutraceuticals
Adequan (Polyglycoaminoglycan) and Cartrophen (Pentosan polysulphate)
These injectables have been used in dogs and are also used in cats. The bioavailability and distribution of PSGAGs to inflamed joints in cats has been demonstrated with extralabel subcutaneous administration.

Dosage: Cartrophen 1 ml per 33kg SQ once weekly for 4 weeks then once monthly
Adequan: 5mg/kg once weekly x 4-6 weeks then q14d then once monthly (SQ)

Omega 3 fatty acids
The primary source of omega 3 fatty acids is fish oil. A recent placebo controlled trial done with Royal Canin’s Feline Mobility support diet found significant improvement in indicators of pain and quality of life when comparing the base-line outcome measures to those collected at the end of the 16-week trial. (Lascelles et al). Dose of combined EPA + DHA is maximum 100 mg/kg if using capsules or adding fish oil to the diet (generally 1 tsp of fish oil is the maximum). There is a concern that this level of
supplementation may cause clotting problems in this species. However, research shows that at this level of supplementation, no cats experienced any clotting problems (Joe Wakshlag, Cornell University, Personal communication)

**Green lipped perna mussel (GLM)**

Perna canaliculus is found in the waters around Australia and New Zealand. It contains EPA, DHA, and ETA. It is also a source of glycoproteins and GAGs. The anti-inflammatory effects of GLM may be derived from its omega-3 fatty acids content or the GAGs or the glycoproteins. Suggested dose is 50-70mg/kg/d

**Herbals**

Flexadin Plus (Vetoquinol) contains Devil’s Claw, Omega 3 and Glucosamine/chondroitin—seems to get a good rating but RCCT lacking.

**Avocado soybean unsaponifiables**

Avocado soybean unsaponifiables (ASU) are residues of avocado and soy oils combined in a 1:2 ratio to produce a product that has demonstrated anti-arthritic properties. Theoretically, ASU decrease the production of pro-inflammatory cytokines such as PGE-2 and TNF alpha. There are no published controlled trials in clinical cats with OA examining ASU alone or in combination products although in vitro studies have been conducted on feline chondrocytes.

**Pain management beyond drugs**

**Weight reduction**

Many cats with OA are overweight. As the OA worsens and becomes more painful the cats become less active contributing to an increase in weight. Excess weight causes an excess load on an abnormal joint, creating more pain. In addition the adipose tissue secretes adipokines which are pro-inflammatory and these increase the overall inflammation in the joint of the cat. Secret to weight loss in the cat is canned weight loss diet amount calculated by RER and exercise.

Determine RER from Body Condition Score on a 9 scale. For every point that the cat is overweight over the ideal 5/9 body condition score, the cat is 10 % obese. For example a 10 kg cat with a body condition score of 7/9 is 2 x 10% or 20% over ideal weight. To determine Lean body weight in kilograms 10/1.20 = 8.3kg. Take this lean body mass of 8.3 and raise it to the 0.75 power. Multiply this result by 70 to give the RER. In this case a cat with a lean body mass of 8.3 kg has a RER of 342 kcal. Multiply this by 0.8 = 272 kcal. This is the number needed for weight loss. Use this formula and this calculation rather than amount on bag or can for weight loss.

Exercise therapy can involve an obstacle course, playing with a feather, chasing a laser pointer, climbing a tower etc. A hockey rink with cat toys on a smooth surface can help with weight loss. Moving the food bowl during feeding and making the cat move around is helpful. Food balls can work for cats as well. Designing a cat tree so the cat has vertical and horizontal space is helpful. Indoor outdoor cats are thinner—cat gazebo is a possibility. Treadmill exercise can also be used for cats. Cat nip treats may entice cats to exercise.

**Acupuncture**

Acupuncture is a safe and often enjoyable method of pain relief for cats and should be considered as part of a multi modal pain management plan. It is minimally invasive and can be used with other modalities and medications as well. This author has used it in cat with back pain, osteoarthritis, stifle pain, post surgery, persistent pain post declaw, for excess grooming (that was related to back pain) for interstitial cystitis and other conditions. There is a growing body of evidence for its use in veterinary medicine.

**Physical rehabilitation**

Physical rehabilitation is now considered a mainstay for pain relief post surgery and for geriatric animals. Cats are very amenable to all forms of physical therapies. Physical therapy should be considered part of a long term strategy for pain management in the cat. The goals of physical therapy are to restore muscular and joint strength and function, to restore balance and proprioception, to relieve pain, to improve mobility, endurance and flexibility.

Physical rehabilitation can involve manual therapies, massage, laser therapy, hot and cold therapy, exercise therapy, joint mobilizations, ultrasound, electrical stimulation, myofascial release and hydrotherapy. Exercise therapies using balls, treadmills and other devices can be used with cats and often are simply limited by imagination. Passive range of motion (PROM) is a technique easily taught to clients to help relieve pain for stiff cats and one that should be employed for every geriatric cat.

**References**


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Myofascial Pain Syndrome (MPS) was brought to the attention of modern human medicine by Dr. Janet Travell in 1952 although it has been described in literature as long ago as the 16th century. Despite this, it has failed to enter mainstream medicine, especially in veterinary medicine. Many veterinarians do not even know of its existence! However, within the past decade this aspect of pain medicine along with many others has been steadily gaining a foothold in the general veterinary practice.

**What is myofascial pain?**

The pathophysiology of myofascial pain is a complex syndrome involving in part, motor, sensory and autonomic nerve components. It is a myalgic condition in which muscle and tendon are the primary cause of pain. The syndrome is centered around the myofascial trigger point (MTrP). A myofascial trigger point is an extended contraction of a few muscle fibers that results in a painful knot. Simons, Travell and Simons define it as

> “a hyper irritable spot in skeletal muscle that is associated with a hypersensitive palpable nodule in a taut band. The spot is tender when pressed and can give rise to characteristic referred pain, motor dysfunction and autonomic phenomena.”

Therefore all MTrPs have a sensory component, a motor component and an autonomic component. When the motor end plate is overstretched which can happen when only a few muscle fibers are activated then myofascial tension is increased in that fiber. An increase of tension of only 1% will evoke a 10% increase in ACh release. With excessive release of ACh there is excessive motor activity. The local muscle contraction compresses local sensory nerves and blood vessels and reduces the supply of oxygen to the area. Decreased oxygen and increased metabolic demands of the contracted muscle fibers result in a depletion of the local ATP. This cause pre and post synaptic changes in the calcium pump and leads to muscle spasms. Trigger points are formed which are painful and either excite or inhibit activity on motor activity in the muscle or its functionally related group. This inhibition causes poor coordination and muscle imbalances. There are also autonomic phenomena associated with MTrPs.

**Etiology of MTrPs**

**Mechanical issues**

Acute trauma may activate MTrPs but does not perpetuate them. Sudden activation can occur with direct trauma, muscle strain, joint sprain or excessive or unusual exercise. Mostly commonly are formed with chronic muscle overload such as occurs with orthopedic injury, neuropathy, joint dysfunction or osteoarthritic pain. It is thought that low level muscle contractions, unaccustomed eccentric contractions or eccentric contractions in unconditioned muscle as well as maximal or sub maximal concentric contractions may lead to MTrP formation.

In OA the joint dysfunction and postural changes can activate and perpetuate MTrPs. With coxofemoral arthritis the muscles that frequently develop trigger points are the sartorius, tensor fascia lata, pectineus, rectus femoris and iliopsoas (hip flexors). Due to the forward weight shift, they also develop in the triceps, infraspinatus and deltoid muscles. Because pelvic movement is compromised, and more lateral flexion of the spine occurs, the iliocostalis lumbarum and lateral multifidi are also effected. If a dog is hopping on one back leg, trigger points can develop in the contralateral limb and hopping causes excessive eccentric contraction of the stifle extensors. In this leg we see MTrPs in the sartorius, tensor fascia latae, rectus femoris and vastus group. The lumbar paraspinals are also involved as they assist in ambulation.

**Nutritional deficiencies and metabolic issues**

It is unknown if nutritional deficiencies or metabolic problems perpetuate trigger points in dogs but in humans they have been linked with certain deficiencies such as cobalamin, folate, iron deficiency, Vitamin D and B12 deficiency and metabolic diseases such as hypothyroidism and diabetes.

**Examination techniques**

MTrPs are diagnosed by palpation. 3 types of palpation are used: Flat palpation, Pincer Palpation and Snapping palpation. With flat palpation the finger pressure is applied at right angles to the muscle fiber compressing against the bone—this is used for the infraspinatus, supraspinatus and psoas muscle. With Pincer Palpation the muscle bands are pinched and rolled between thumb and fingers to detect taut bands. This works for the triceps, sartorial and tensor fascia latae. Snapping palpation is similar to pincer but the fibers are rolled under the finger similar to plucking a guitar string. Taut bands are palpated and usually animal is painful so jumps (Jump sign)
Clinical cases

**Brooklyn the Rottweiler**

F/S 5 year old Rottweiler BCS 6/9, had TPLO LH 1 year ago and still not using leg well. Current pain medications included Meloxicam and Tramadol. On examination she had a large number of MTrPs in her iliopsoas, sartorial, TFL on the left side and Triceps bilaterally. All of her hip flexors were sore to the point she resent extension of her stifle and was vocal and aggressive with the iliopsoas test. Because Brooklyn had spent a lot of time with her leg contracted she had slight muscle contractions of the hip flexors due. The front leg MTrPs were due to compensation from weight shifting. Brooklyn was uncomfortable and her owners were frustrated.

Treatment: Sedation and dry needling

After one session Brooklyn was more comfortable and would allow her muscles to be touched. A rehabilitation program including acupuncture, UWTM, stretching, leg and core strengthening was able to proceed. Within 1 month Brooklyn was back to her normal self and was fully weight bearing.

**Regi the wirehaired fox terrier**

Regi, 11 yr old F/S BCS 6/9 former agility dog, pain in sacral area, elbow arthritis, lagging in walks and not wanting to go many places. Owner felt she was depressed. She noticed Regi was walking “funny” in the front end and base wide in the hind end. She had had several rehabilitation sessions for strengthening and gait retraining as well as medication—Gabapentin, Amantadine, Chinese herbs, acupuncture—nothing seemed to be helping. My examination revealed myofascial pain in her iliopsoas, quadriceps, and sartorial and in the triceps and infraspinatus muscles of both front legs.

Treatment: Sedation and dry needling

Result: Regi continued rehab therapy but this time there was a big improvement. She went back to walking well and was no longer depressed.

Dry needling is the preferred method of treatment in myofascial pain syndrome in dogs. Dry needling involves the act of placing an acupuncture needle directly into the painful trigger point resulting in a complex cascade of events involving in part spinal reflexes, increased blood flow and an increase in the amount of energy available to the muscle. This causes the taut band of muscle containing the trigger point to relax and the pain relief is immediate. When Brooklyn’s owner picked up her dog after the first session, she was misty-eyed with relief when she saw Brooklyn walking normally as she came out to greet her. Dry needling imparts an immediate benefit but it generally requires several sessions to give complete relief. And unless the underlying cause can be found and completely treated, it eventually returns needing additional treatments, especially in the case of chronic conditions like osteoarthritis.

Dry needling is not taught in university settings. The only regular classes that a veterinarian can take is through the Canine Trigger Point Therapy Program given through Myopain Seminars and taught by Drs. Jan Dommerholt and Rick Wall.4

References

Nutraceuticals for Pain
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What is a nutraceutical?
A food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease.

What is a dietary supplement?
Product taken by mouth that contains a dietary ingredient intended to supplement the diet or a substance produced in purified or extracted form which, when administered orally to patients, aims to provide them the necessary elements for their structure and normal function to better their health and wellbeing.

Nutraceuticals are used by a large number of veterinary clients for osteoarthritis and are one of the fastest growing areas of supplementation for pets.

Normal joint structure and function
The ECM of articular cartilage is mostly protein and water and has both interfibrillar (ground substance) and fibrillar components. The fibrillar component is composed of mostly collagen and elastin. Collagen is the most abundant protein in the body, has a tensile strength similar to steel, is responsible for the integrity of the tissues and their resistance to tensile forces. The interfibrillar component is mostly glycoproteins and proteoglycans (PGs)

Proteoglycans provide the articular cartilage with selective permeability properties and compressive stiffness, while the collagen fibers provide tensile strength.

Proteoglycans have a negative charge & great affinity for water and have the potential to absorb 50 times their weight in water. However, the collagen framework in normal cartilage constrains the proteoglycans and limits their ability to expand to about 20% of their potential. This swelling pressure keeps the cartilage turgid, helping to resist deformation when a compressive load is applied. This dynamic tissue is able to tolerate both compressive and shearing forces without damage, transmitting and distributing the forces to the underlying subchondral bone, which aids in shock absorption.

The proteoglycans in articular cartilage are large aggregates of protein, hyaluronic acid and glycosaminoglycans, predominantly chondroitin 4-sulfate, chondroitin 6-sulfate, and keratan sulfate.

Glycosaminoglycans (GAGs) are long unbranched polysaccharides consisting of a repeating disaccharide unit. This unit consists of an N-acetyl-hexosamine and a hexose or hexuronic acid, either or both of which may be sulfated. The combination of the sulfate group and the carboxylate groups of the uronic acid residues gives them a very high density of negative charge. Members of the glycosaminoglycan family vary in the type of hexosamine, hexose or hexuronic acid unit they contain (e.g. glucuronic acid, iduronic acid, galactose, galactosamine, glucosamine). They also vary in the geometry of the glycosidic linkage (N or O linkage) GAG chains covalently linked to a protein to form proteoglycans.

Extensive notes on the pathogenesis of osteoarthritis have been provided for a previous lecture but to review the pathogenesis of osteoarthritits on a cellular level, stresses on the joint lead to production of inflammatory cytokines released by synovial cells, chondrocytes, macrophages and fibroblasts. These proinflammatory cytokines, including certain interleukins and TNF-alpha, lead to upregulation of COX-2 enzymes and production of eicosanoids such as PGE2,and the upregulation of matrix metalloproteinases. Normally during metabolism PGs are broken down by enzymes matrix metalloproteinases (MMPs) and aggrecanase. In acute inflammation MMPs increase in number and disrupt the balance of production and destruction in the joint. There is shift toward breakdown of articular cartilage resulting from an imbalance between MMPs and their TIMP inhibitors, leading to thinning and destruction of the cartilage tissue and perpetuation of the inflammatory cascade with PGE2 production and subsequent pain. On a gross level, the thinning or loss of cartilage leads to joint space narrowing, remodelling of subchondral bone with sclerosis and osteophyte formation, joint effusion, periarticular swelling and pain which may lead to decreased use of the joint and secondary atrophy of musculature.

Goals for a nutraceutical to relieve OA pain
1. Decrease in inflammatory prostaglandin (PGE2).
2. Decrease the production of Pro MMP 2 & 9 and active MMP 2 and 9 (the enzymes responsible for degradation of cartilage).
3. Increase the inhibitor of MMP (TIMP-2) to help restore proper balance between these enzymes.
Evidence based nutraceutical use
Fish oil—Omega 3 DHA and EPA

Arachidonic acid (AA) is the primary substrate for the lipooxygenase and cyclooxygenase enzymes. This fatty acid is derived from dietary sources and stored in phospholipids of the cell membrane until needed. AA is a member of the omega-6 fatty acid family. AA can be partly replaced in cell membranes by the omega-3 fatty acid Eicosapentanoic Acid.

The difference between omega-6 and omega-3 fatty acids centers on the location of the first double bond in the carbon chain, occurring either at the 3rd or 6th carbon from the methyl end. While mammalian cells can elongate and desaturate fatty acids, they are not able to form double-bonds beyond these defining bonds, so are unable to synthesize these fatty acids nor interconvert between these families. Thus, the presence of these fatty acids within cell membranes reflects dietary intake. And this can be important because the physiologic function of the 2 fatty acid families differ.

Eicosanoids are metabolically active compounds derived from 20-carbon fatty acids, usually arachidonic acid. The lipooxygenase (5-LOX) and cyclooxygenase (COX) enzymes are the rate-limiting steps in the production of leukotriene B4, thromboxane A2 and prostaglandin E2. In health, these eicosanoids serve important functions. However, in inflammatory conditions such as arthritis, their production can be increased and their effects can be detrimental. For example, PGE2 can be increased up to 50 fold in arthritic joints. Leukotriene B4 has a potent chemotactic effect and promotes further inflammation. PGE2 and TXA2 both promote the release of tumor necrosis factor alpha and Interleukin 1 beta, both which promote further inflammation and, in joints, stimulate the production of matrix metalloproteinases or MMPs. MMPs are the collagen-destroying enzymes that break down articular cartilage in arthritic joints. Further, PGE2 is a potent stimulator of pain receptors, and contributes to the pain of arthritis.

Eicosapentanoic acid (EPA) also can be used by the LOX and COX enzymes to produce eicosanoids. However, when EPA is used by the COX and LOX enzymes, they produce the eicosanoids PGE3, thromboxane (TX) A3 and LTB5, which are less active and relatively anti-inflammatory compared to their counterparts produced from AA.

It has been demonstrated that therapeutic diets containing approximately 3.5% omega 3 fatty acids can decrease pain and lameness, improve weight bearing, and decrease the need for NSAIDs in dogs with OA. The primary source of omega 3 fatty acids is fish oil. Approximately 480 mg/kg of fish oil (50–100 mg/kg EPA) would be required as a supplement to match the amounts available in the therapeutic food discussed above. A recent placebo-controlled clinical trial in dogs with OA investigated the effects of a fish oil supplement added to a non-fish based food, dosed at 90 mg/kg EPA and 20 mg/kg DHA. These researchers found significant improvement in indicators of pain and quality of life when comparing the base-line outcome measures to those collected at the end of the 16-week trial. There is a high level of support for supplementation of omega 3 fatty acids.

Mobility diets
All mobility diets are not created equal! Research shows that 7.5 g EPA +DHA/1000kcal diet significantly reduced symptoms of arthritis. This amount is quite unwieldy as well as likely to cause diarrhea. Other studies have shown as little as 1 to 3 g/1000kcal has clinical effect. Ideally for most dogs you would like to get up to the 100mg/kg of Omega 3 for arthritis. Here is an example:

For a 20kg dog you would like it to receive 2 g of Omega 3 total/day for arthritis. This dog would eat around 700 kcal so if feeding a 1.5 g Omega 3/1000kcal diet it would provide approximately 1 gram of Omega 3. To make up the additional gram, you would have to supplement with 2 capsules that contain 500mg of EPA and DHA combined. This is quite feasible.

Green-lipped mussel
Perna canaliculus is found in the waters around Australia and New Zealand. It contains EPA, DHA, and ETA. It is also a source of glycoproteins and GAGs. A randomized, double-blind, placebo controlled clinical trial in dogs with chronic pain attributed to OA found significant improvement in mobility and pain in those dogs treated with GLM compared to placebo. The dose used was 50 mg/kg. The anti-inflammatory effects of GLM may be derived from its omega-3 fatty acids content or the GAGs or the glycoproteins. This has yet to be determined but it does prove to be at least mildly effective.6,7

Avocado/soybean unsaponifiables
Avocado soybean unsaponifiables (ASU) are residues of avocado and soy oils combined in a 1:2 ratio to produce a product that has demonstrated anti-arthritic properties. Theoretically, ASU decrease the production of pro-inflammatory cytokines such as PGE-2 and TNF alpha. In a canine cruciate ligament transection model, ASU administration decreased osteophytes, improved cartilage thickness and produced more normal chondrocytes.11 Additional in vitro studies have shown that the combination of ASU with chondroitin is more effective in decreasing inflammatory cytokines than either product alone. There are no published controlled trials in clinical dogs with OA examining ASU alone or in combination products. However research on induced arthritis shows a positive result. Dasuquin (Nutramaxx) is the product generally used.

Chondroprotectants
Glucosamine/chondroitin
Glucosamine is a precursor of glycosaminoglycan (GAG). When administered orally, glucosamine is 90% absorbed and undergoes biotransformation in the liver. It is then distributed to tissues and has been shown to have a tropism for articular cartilage. Glucosamine sulfate is absorbed better than glucosamine hydrochloride and may be more effective.
The mechanism of action of glucosamine has not been fully elucidated. In vitro studies have shown that when exogenous glucosamine is administered, it is utilized in the synthesis of GAGs. It has also been demonstrated that supplementation with glucosamine inhibits enzymes that are responsible for the degradation of cartilage, and the production of inflammatory mediators is decreased.

Chondroitin sulfate is a much larger molecule than glucosamine, and its oral bioavailability has been questioned. Low-molecular weight chondroitin sulfate is more effectively absorbed by the gastrointestinal tract than larger molecules. Metabolites of chondroitin sulfate are concentrated in articular cartilage. The mechanisms of action of chondroitin are: to stimulate GAG production; inhibit degradative enzymes; enhances the production of hyaluronic acid and prevent the degeneration of type II collagen within articular cartilage. Glucosamine and chondroitin sulfate are often combined in commercially available products. It appears that there is a synergistic effect when the two products are used together.

Studies demonstrating efficacious use of glucosamine/chondroitin are few. McCarthy et al showed glucosamine/chondroitin improved pain, weight bearing and disease severity scores (3/5 measures) but the onset of response was slower for glucosamine/chondroitin compared to NSAIDs. Moreau et al showed no change with the supplement so evidence is conflicting. In a systematic review only 13 studies were controlled and evidence was positive for Glucosamine/chondroitin but this is a human study. The level of evidence supporting the use of glucosamine/chondroitin for pain management in dogs is low.

Dosage: Dose at 15mg/kg on the Chondroitin fraction.

Adequan
Polysulfated glycosaminoglycans (PSGAGs) are a semisynthetic product (derived from bovine trachea) structurally similar to the GAGs found in articular hyaline cartilage. PSGAGs stimulate collagen synthesis and inhibit collagen breakdown as well as decrease pain and inflammation. Several studies have documented positive effects when administering PSGAGs (Adequan) to dogs with hip dysplasia and osteoarthritis. One study found decreased hip laxity in dogs treated with Adequan twice weekly from 6 weeks to 8 months of age compared to age-matched controls. It is recommended to begin treatment as early in the disease process as possible in order to slow the progression of cartilage damage. The strength of evidence for PSGAGs used at the labeled dose is considered high. Dose: 5mg/kg once weekly x 4 to 6 weeks then once monthly in dogs, cats first 4 weeks is the same but 2nd month every other week then once monthly.

Cartrophen
Pentosan polysulphate—this product is used in Canada, Europe and Australia. Similar actions to Adequate. Dose is 1ml/33kg once weekly for 4 weeks then once monthly.

Herbals and natural supplements

Flex-RX
This product is a bioflavanoid that contains Baicailin and Catechin and has balanced COX and 5-LOX enzyme inhibition activity. In studies by Burnett et al it showed statistically significant improvement in pain scores when compared to Cosequin using veterinarian and owner VAS.

Elk velvet antler
Quality Elk Velvet comes from the antler at the velvet stage and contains Chondroitin Sulphate, collagen, glycosaminoglycan and pilose antler peptide. Study by Morneau showed improvement in dogs with clinical OA on force plate and by subjective analysis.

Boswellia
This is also known as Indian Frankincense in Ayurvedic Medicine. 4 compounds isolated have been isolated and purified. These have been found to have anti-LOX activity.

This herb is found in human products Flexamine as Aflapin and Osteo-biflex as 5-Loxin.

2 Placebo controlled clinical trials in humans suggest efficacy for joint pain. In an unblinded open label Austrian study it was found to have 71 percent positive response in clinically lame dogs.

Theracurmin
Curcumin is found in veterinary nutraceuticals marketed for arthritis. Its utility as a natural NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and cyclooxygenase-2 inhibitor is documented in humans but not in dogs. However, its gastrointestinal absorption in most species appears to be poor. An extract of turmeric, the spice from which curcumin is derived, produced subjective, but not objective, improvements in dogs with arthritis. Theracurmin is a new water soluble curcumin that has shown to have advantages and may have promise in the future in dogs.

References