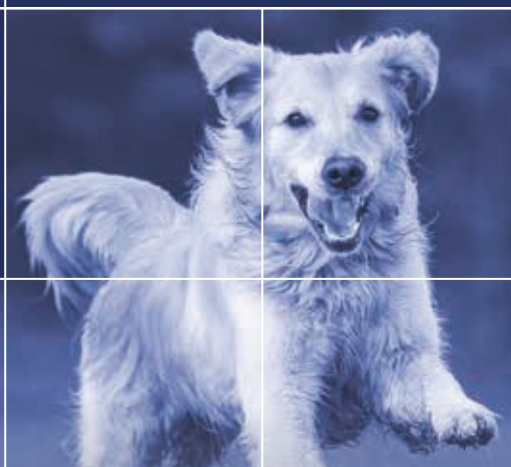
VetPlus Clinical Focus



What is new in the management of chronic degenerative joint disease in dogs: the role of the multimodal management and the pharmacological and non-pharmacological treatment.

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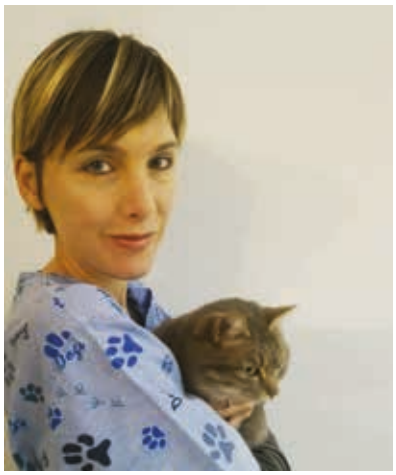

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Chronic Pain in Pets

The prevention, recognition, and treatment of chronic pain in pets represent key issues in the context of clinical activity of today veterinary medicine.

Unlike the post-surgical pain, easily predictable from the vet's point of view and of which even the owner has clear perception, the osteoarticular pain, with which many dogs and cats live together, has more ambiguous aspects, with the risk of being sometimes misunderstood or under-diagnosed.

Changes in mood or in the character, or even exaggerate behavioural reactions, may conceal a state of painful discomfort associated with degenerative joint disease (OA).

OA needs to be recognized since the early stages of onset, in order to improve the quality of life of our pets, reduce the rate of progression of otherwise highly disabling conditions, and increase compliance with the customer-owner. The OA management runs through the use of pharmacological and non-pharmacological treatments.

The acronym PLATTER (Plan, Anticipate, TreaT, Evaluate and Return) summarizes the appropriate algorithm of the pain treatment according to the guidelines of 2015 of the American Animal Hospital Association (AAHA) and the 'American Association of Feline Practitioners (AAFP) (Epstein et al, 2015).

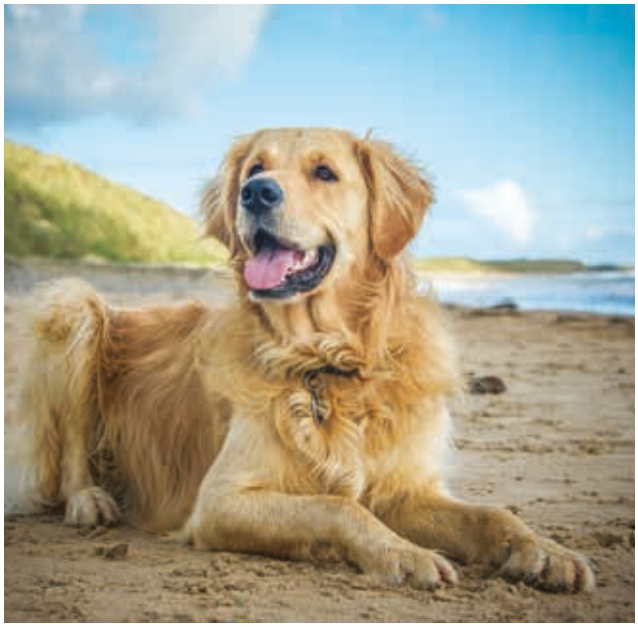
As part of a multimodal and, therefore, interdisciplinary management, in the patient suffering from osteo-articular pain, conventional drug therapy, mainly non-steroidal anti-inflammatory (FANS), should be accompanied by "complementary" treatments (e.g. controlled movement and physiotherapy exercises, feeding and weight control, cold compresses, nutraceuticals) for which there is increasing scientific evidence (Comblain et al, 2016).

Chronic pain is defined as a pain which persists beyond the normal period of recovery or even in conditions in which the recovery is not complete or will not occur at all (Epstein et al, 2015).

A multimodal approach to the patient with OA can reduce the potential side effects associated with the use of a single molecule and act at the level of different receptors and pain pathways.

Pharmacological Management

For many years the pillar in the medical treatment of osteoarthritis has been the use of NSAIDs, which acts by inhibiting the formation of COX enzymes necessary for the formation of Prostaglandins and Thromboxane. PGE



2, the better represented prostaglandin at the level of synovial cells, acts by inducing vascular dilation, by enhancing the release of inflammatory mediators and by hyper-sensitising pain receptors.

Next to selective anti-inflammatory COX-2, which are enzymes that have also a constitutional role for that concerns key organs, molecules such as the grapiprant, even more selective if compared to PGE2 receptors, have been recently developed (Rausch-Derra LC et al. 2015).

A review paper of 2007, given the wide availability of medical alternatives and the difficulty for vets to orient themselves critically in order to undertake the proper therapeutic procedure, evaluated more than 300 scientific publications on OA treatment in dogs and cats. It concluded that there is a scientifically validated literature and a high level of comfort in suggesting the use of NSAIDs such as meloxicam (Aragon et al. 2007).

Alongside there is a literature based on clinical trials often missing objective scientific assessments, such as those produced by some studies that evaluated the effectiveness of taking Pentosan polysulfate, turmeric extracts, or Perna canaliculus (Aragon et al. 2007). Although for some of these molecules the data were promising, until objective trial data exists, the authors do not currently recommend these molecules.

Even opiates, local anaesthetics and molecules such as tramadol, amantadine, gabapentin and tricyclic antidepressants are used in the management of chronic pain of neuromuscular origin.

Local Drug Therapies

There are no definitive data in veterinary medicine regarding the use of intra-articular corticosteroid administration, although treatments with methylprednisolone sodium acetate and triamcinolone have shown beneficial effects in dogs in several clinical trials (Vandeweerd et al. 2015).

PRP Products (Platelet Rich Plasma), defined as concentrated autologous compounds of platelets for an intra-articular or intra-lesional use, have been introduced since the beginning of 2000. The premise behind the use of these products, whose circulation has been too rapid, is based on the function of platelets that seem to play a role not only in the mechanisms of the haemostasis but also in the tissue anabolic processes, in revascularization and inflammation reductions, also at the level of the bone tissue. A significant variability exists in terms of final concentration of platelets and leukocytes for the several products on the market (Franklin et al. 2015).

At the moment, clarity about mechanisms of action, therapeutic levels, applications and clinical efficacy, as well as a greater standardization in the methods of preparation and control of the quality of the final product, seem really desirable (Conzemius, 2014).

Non-Pharmacological Management

As OA acts as a chronic disease requiring long term administration, dietary supplements has the undeniable advantage of reduced or either absent adverse effects compare to drugs.

A recent review (Comblain et al, 2015) about dietary supplements for the management of OA in dogs has reported the following results: contrasting results, lack of data and low bioavailability for oral curcumin; same lack of data for Avocado–soybean unsaponifiables; positive effect in terms of pain score improvements for chondroitin sulphate and glucosamine sulphate (McCarthy et al., 2007; Altilio et al., 2007; Gupta et al., 2012) except than for the results of Moreau study (Moreau et al. 2003).

Plasma concentrations of inflammatory markers such as arachidonic acid, IL-1, IL-6 and PGE2 appears reduced in dogs receiving diet with Omega 3 EFAs. Perna Canaliculus as well when added to the daily food intake seems having beneficial effects, which required further investigations as some studies results needs cautious evaluation.

Analgesic effects similar to those obtained with traditional NSAIDs were observed in dogs with chronic pain when undergoing experimental intravenous treatment with anti-nerve growth factor antibodies (NGF) (NV-01) (Lascelles et al. 2015).

Nutrition and Weight Management

The adipose tissue acts as organ secreting cytokines, inflammatory mediators. The reduction of the food share of 25% delays the onset and reduces the effect of osteoarthritis in dogs (Smith, 2006). A balance between omega 3 fatty acids and omega 6 fatty acids is essential to the formation of pro and anti-inflammatory lipids. Omega-3s, in particular, induce the formation of eicosanoids with lower inflammatory power than those that originate from

arachidonic acid, resulting from omega-6s. The experimental incorporation of omega-3 fatty acids to the membranes of articular chondrocytes has induced the following dose-dependent effects: the reduction of the expression and the activity of degrading enzymes of the proteoglycans and the reduction of expression of proinflammatory cytokines such as IL1 alpha, TNFalpha and COX2, without any alteration in the expression of COX1 (Corbee, 2013).

The richest sources of animal omega 3 fatty acid are fish oil and krill oil, as well as for the vegetal source flax oil, nuts and algae.

In an experimental study on mice with rheumatoid arthritis, the supplementation of essential omega 3 fatty acids in the diet reduced the serum concentration of inflammatory mediators (Curtis et al. 2000).

A study showed the effectiveness in dogs with OA of the short-term administration of fish oil, naturally rich in docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), both omega-3 fatty acids.

The results indicated a significant increase in the load on the limbs (peak vertical force) measured by analytical assessment of gait and a probability to present a gait improvement during the 90 days of dosing which was 7 times higher than the control group (Roush 2010).

In humans, a dietary supplementation with Omega 3 EFAs (1000-2000 mg daily) brought to clinical improvement in patients with slight to moderate OA of the knee (Peanpadungrat P. 2015).

Physiotherapy

In obese patients, weight loss together with physiotherapy (walks on a leash, massage, acupuncture, passive joint movement) gives as result an improvement of the clinical symptoms associated with OA (Mlacnik et al. 2006, Impellizeri et al. 2000). In addition to pain reduction, the purpose of the processing is to re-establish a joint and muscle function. Manipulative techniques can be combined with electric therapies such as neuromuscular electrical stimulation (type Transcutaneous Electrical Nerve Stimulator, or TENS) and Shock waves (Extracorporeal Shockwave Therapy, or ESWT) (Mueller et al. 2007, Becker et al. 2015).

Nutraceuticals

The Pentosan Polysulfate, available in an oral association combined with calcium, shows a beneficial effect on the synthesis of hyaluronan and reduces the loss of proteoglycans at an articular cartilage level.

However, as for shellfish in green shell and turmeric extracts, Aragon et al. pointed out, at the time of the study, that the data were not sufficient to recommend, with a high confidence index, the use of these substances in patients with OA. Promising data on the use of glucosamine hydrochloride and chondroitin sulphate were published as previously mentioned.

Glucosamine is a soluble in water amino-monosaccharide which, once turned into N- acetyl glucosamine, acts as a precursor for glycosaminoglycan (GAG), the components of the extracellular matrix of the articular cartilage. The absorption is about 90% orally, with a pKa that favours intestinal absorption, a rapid tissue spread and a particular tropism for articular cartilage (Neil et al. 2005).

Chondroitin sulphate, which is a normal constituent of joint cartilage, demonstrates similar characteristics. Form, origin and weight will influence the absorption (bioavailability up to 70%) after oral administration, with an increased gastrointestinal permeability of the chondroitin sulphate with a low molecular weight (Neil et al.2005).

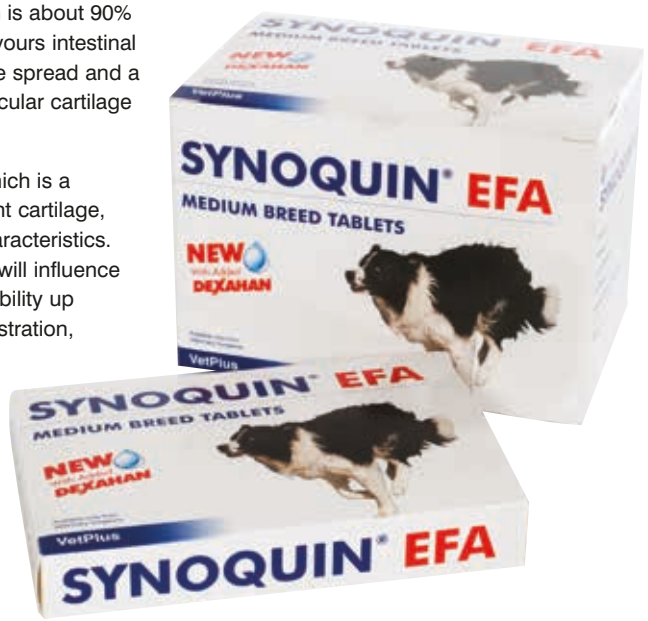
Tropism for the articular cartilage is the cause of the higher concentration in this seat rather than in the plasmatic one. The chondroitin sulphate plays a role in maintaining the viscosity of the synovial fluid and, in combination with glucosamine, has demonstrated to have beneficial effects for the protection of joint cartilage and the reduction of the need to count on pharmacological treatment with NSAIDs in subjects suffering from mild to moderate OA (Neil et al. 2005, Johnson et al. 2001).

In order to summarize the data from the research in human medicine in patients undergoing treatment with chondroitin sulphate and glucosamine, a meta-analytical study has shown beneficial effects in terms of pain reduction and improvement of the ability of movement in 14 of 15 studies (McAlindon et al, 2000).

Conclusion

The joint chronic pain occurs as a progressive phenomenon whose evolution is able to affect significantly the quality of life of dogs and cats. The prevention, recognition and treatment of joint chronic pain must therefore be primary objectives within the clinical activity of the vet.

In the veterinary facility, strategies that reduce anxiety and nervousness should be adopted in individuals with OA, for which the gentle manipulations and lack of physical obstacles within the cages can be a clear aid. In addiction, the education of the owner-customer has a prime role in the management of chronic disease at home. Constancy and regularity of care, in a non-stressful but comfortable environment, can improve the everyday lives and the level of relationship of dogs and cats with OA.



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