Chronic pain in cats and dogs: management and treatment

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ABSTRACT

Chronic pain is complex and understanding and assessing the pain with appropriate scales is necessary for a successful treatment. NSAIDs are still the first line medications and only licensed drugs for long-term use. Other drugs, such as tramadol, gabapentin and amantadine, are useful to manage central sensitisation and neuropathic pain.

Non-medical management, such as physiotherapy, hydrotherapy, acupuncture and weight management, is integral for long-term management of chronic pain. Overall, multimodal management is essential to a successful outcome.

Chronic pain is described, in human beings, as a state of pain that lasts beyond the acute phase of the underlying disease or disorder causing it, whether persisting (such as osteoarthritis; OA or cancer) or resolved (such as a postoperative period).

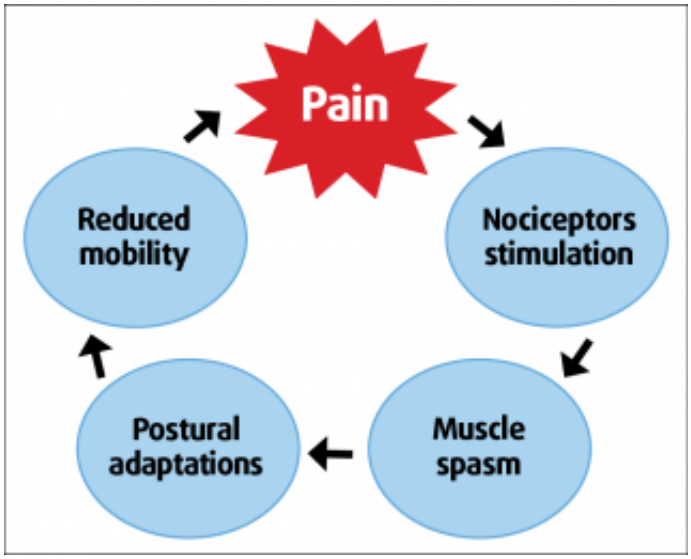

Figure 1. Pain cycle. When a painful stimulus irritates the nociceptors, spasm of the surrounding muscles occurs, leading to local and distant postural adaptations and reluctance to move, thus increasing nociceptor stimulation and feeding the pain cycle.

Chronic pain is difficult to both characterise and treat, and remains a major health concern, with a prevalence of 10.1% to more than 50%, depending on the studies (Voscopoulos and Lema, 2010). Similarly, chronic pain is increasingly being recognised in small animals, although its prevalence is still unknown (MacFarlane et al, 2014).

Pain can be characterised as being:

- Nociceptive (peripheral inflammatory pain).
- Neuropathic (pain arising from direct nerve damage).
- Centralised pain (pain arising from sensitisation at the level of the spinal cord mainly; Ablin and Buskila, 2015).

Most patients, however, will suffer from a combination of these pains, hence the concept of multimodal pain management. Recognising the origin(s) of the pain allows us to choose the treatment more accurately, hopefully leading to a more successful outcome.

For example, a dog with chronic OA will most likely suffer from low-grade inflammatory pain, but may also have centralised pain from the chronic stimulation of the peripheral nociceptors and/or neuropathic pain.

The clinical signs of chronic pain are usually subtle. Changes in behaviour (such as being less interactive, depressed, aggressive or reluctant to touch) are often described by owners.

Changes in daily activities (such as difficulty in rising, climbing stairs or running) leading to a

generally reduced mobility are also good indicators of chronic pain. Lameness is common in dogs, but rare in cats (Slingerland et al, 2011; Fox and Mills, 2011).

As animals cannot describe their pain, we must rely on our interpretation and subjective and objective measures of pain. A few chronic pain scales are available that allow a more objective measurement of the state of pain and are particularly useful to monitor the effect of the treatment. A pain index has also been validated in cats (Gruen et al, 2014).

Medical management

NSAIDs

NSAIDs are still first line medications for chronic pain in small animals. They interfere with production of inflammatory prostaglandins by more or less selective inhibition of the cyclooxygenase-2 (COX-2) enzyme. This leads to a peripheral anti-inflammatory effect on the target tissue and a reduced sensitisation within the CNS. They also are the only licensed medications for long-term use in dogs (MacFarlane et al, 2014; Budsberg, 2014).

Table 1. Dosage and formulation of common cyclooxygenase-2 selective NSAIDs

Name	Dosage in dogs	Dosage in cats	Formulation	Side effects
Carprofen	2.2mg/kg bid or 4.4mg/kg sid PO 4.4mg/kg once SC	Licensed only for perioperative injection (4mg/kg)	Tablets, injectable SC	Increased liver enzyme, idiosyncratic hepatotoxicosis (very rare, <0.06%), dermatologic changes
Meloxicam	0.2mg/kg injection followed by 0.1mg/kg sid PO	Perioperative: 0.1mg/kg to 0.3mg/kg once, then 0.05mg/kg sid PO	Injectable SC, IV Oral suspension	Gastrointestinal (GI) signs, inappetence
Cimicoxib	2mg/kg sid PO	Not tested	Tablets	Limited data
Firocoxib	5mg/kg sid PO	Not tested	Tablets	GI signs, inappetence
Robenacoxib	1mg/kg sid, PO Perioperative: 2mg/kg once	1mg/kg sid PO Perioperative: 2mg/kg once SC Licensed only for 11 days	Tablets	Mild GI signs
Deracoxib	1-2mg/kg sid PO	Not tested	Tablets	GI signs, potentially serious
Mavacoxib	2mg/kg PO repeated 14 days later, then monthly	Not tested	Tablets	Limited data

(Budsberg, 2014; Fox and Mills, 2011)

Table 1. Dosage and formulation of common cyclooxygenase-2 selective NSAIDs.

No particular compound has been proven to be superior to the others, so the choice is down to the clinician based on COX-2 selectivity, side effects, previous adverse reaction to another compound, ease of administration and so on (**Table 1**). In absence of a positive response, it is reasonable to swap for a different one, as the clinical response may vary considerably between individuals. The recommended wash out period is five days to seven days (Fox and Mills, 2011; MacFarlane et al, 2014).

Meloxicam is licensed for long-term use in cats in the UK. It is recommended to withdraw after 14 days if no improvement is noted. Recent studies also suggest robenacoxib may be safe (Budsberg,

2014; King et al, 2015).

Opioids

Tramadol is a synthetic atypical opioid that acts by activation of the mu receptors and inhibition of serotonin and noradrenaline reuptake. The metabolism into the active opioid compound M1 in dogs leads to low blood levels, especially with the sustained release formulation, which may explain the extreme variability of individual response (MacFarlane et al, 2014; Epstein, 2015).

Thus, the positive response to tramadol may be more related to its non-opioid effects and interference with central sensitisation. Nonetheless, it can be an effective drug for mild to moderate pain – especially in cases of chronic pain.

In cats, the biotransformation into the M1 metabolite is significantly higher than in dogs, leading to a genuine opioid effect in this species. However, its bitter taste makes it difficult to administer (Robertson, 2015). The recommended dosage is 2mg/kg to 4mg/kg
twice a day to four times a day in dogs and 2mg/kg to 4mg/kg in cats twice a day.

Paracetamol

Paracetamol acts similarly to non-steroidal medications, with both peripheral and central effects, but its precise mechanism of action is still unknown. It is widely used for mild to moderate pain in humans. Paracetamol is only licensed for use in dogs in a formulation combined with codeine for five days (MacFarlane et al, 2014). However, owing to its mild side effects, it may be safe to use long term. As in humans, it may be safe to use in combination with NSAIDs. The recommended dose is 10mg/kg twice a day.

Alternative drugs

None of the following alternative drugs are licensed for use in small animals, so any use would be under the cascade.

Amantadine

Amantadine was initially developed as an antiviral drug in humans. Among other therapeutic effects, it acts as an N-methyl-D-aspartate (NMDA) receptor antagonist. These receptors play a key role in central sensitisation and pain “wind up” in the dorsal horn of the spinal cord. Therefore, amantadine can be prescribed to reduce central sensitisation in cases of chronic pain.

Lascelles et al (2008) found a positive effect of administration of amantadine in combination with NSAIDs in dogs with OA pain. The recommended dose is 3mg/kg to 5mg/kg once a day. Side effects include sedation, restlessness and induction of emesis (dopaminergic effect; Gaynor and

Muir, 2015; MacFarlane et al, 2014).

Gabapentin

Gabapentin was initially developed as an anticonvulsant. Although a structural analogue to the gamma-aminobutyric acid neurotransmitter, it appears to have antinociceptive effects via a reduction in other excitatory neurotransmitters, such as glutamate and substance P (Gaynor and Muir, 2015).

It is useful in managing chronic pain due to neuropathic pain and/or central sensitisation. The recommended initial dose is 2.5mg/kg to 10mg/kg twice a day to three times a day. Initiating therapy with small doses and increasing gradually to therapeutic effect is less likely to induce sedation. Doses can be increased up to 50mg/kg twice a day to three times a day.

Side effects include sedation, weakness and mood swings (humans). Due to the exclusive renal elimination, care must be taken when given to animals with renal insufficiency and dosage adapted accordingly.

Amitriptyline

Amitriptyline is a tricyclic antidepressant widely used in humans for management of neuropathic pain. Its effects are mostly central on opioid receptors and as a noradrenaline and serotonin re-uptake inhibitor. Anecdotally, it has been used to treat neuropathic pain in dogs (Cashmore, 2009). The recommended dose is between 0.25mg/kg and 2mg/kg once a day to twice a day. It may be prescribed in cats as well, with minimal side effects (such as sedation and urinary retention; Murrell, 2013).

Nutraceuticals

Nutraceuticals aim at modifying the disease process of OA. Despite being widely used and prescribed, good quality evidence of their efficacy is still lacking. The main body of evidence in small animals appears in favour of oral supplementation with omega-3 fatty acids, such as eicosapentaenoic acid and docosahexaenoic acid, found in good qualify fish oils and green-lipped mussel (*Perna canaliculus*) extracts (Fritsch, 2010; Rialland, 2013).

A few veterinary prescription foods include such extracts in their mobility-promoting diets. One study recommended a dosage of 20mg/kg/day to 50mg/kg/day of green-lipped mussel extract as a loading dose (Hielm-Bjorkman et al, 2009). Other food supplements, such as glucosamine, chondroitin, elk velvet antlers, hydrolysed collagen and turmeric, have more anecdotal evidence.

Non-medical management

When it comes to chronic pain, many adjunctive therapies may be useful for long-term management and aim to alleviate pain by breaking down the “pain-spasm-pain” cycle (**Figure 1**). Treating not only the pain, but also its consequences, can significantly improve quality of life.

Physiotherapy

Thermotherapy

Heat therapy is widely used in humans as an adjunctive therapy to alleviate mild chronic pain. A study compared the application of a commercial low heat pack to ibuprofen for management of low back pain and found the heat pack to be superior (Nadler et al, 2002).

Commercial heat packs (unscented microwavable wheat bags, for instance) are easily available and can be recommended to owners with obvious precautions to avoid burns. Heat can be applied for up to 30 minutes at a temperature of 38°C to 40°C to promote muscle relaxation, increase local blood flow and decrease tissue stiffness. Ice packs may be used in cases of acute or chronic pain, for 15 minutes to 20 minutes, wrapped in a thin, moist cloth.

Physiotherapy per se

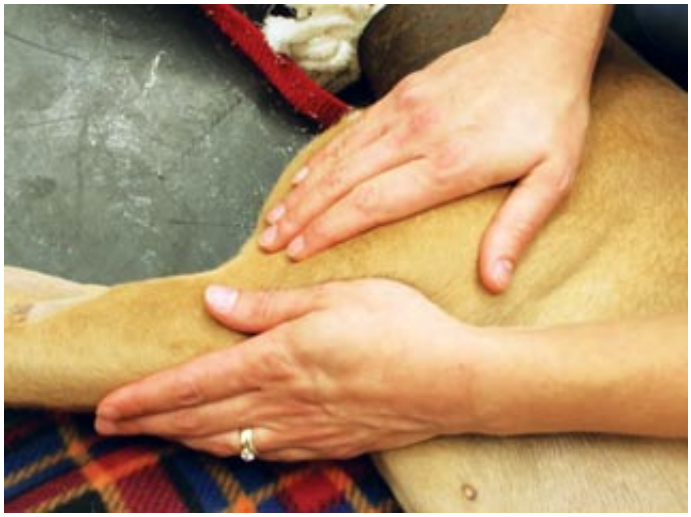

Figure 2. Physiotherapy aims to alleviate impairments and promote mobility.

Physiotherapy aims to alleviate impairments and promote mobility via three main groups of treatments:

- Hands-on therapies (such as massage, trigger point release, joint mobilisations and stretches).
- Physiotherapeutic modalities (such as ultrasound therapy, laser therapy and transcutaneous electrical nerve stimulation).

- Therapeutic exercises (**Figure 2**).

Although strong evidence is still lacking for some of these techniques, it is widely accepted a physiotherapeutic approach is beneficial for the long-term management of chronic pain and can significantly improve mobility in most patients (Fox and Mills, 2011; Chow, 2009; Millis, 2015).

The veterinary physiotherapist examines the patient as a whole and designs a plan tailored to its specific needs. Before referring to a physiotherapist, vets should check his or her qualifications (for instance, via the Association of Chartered Physiotherapists in Animal Therapy or National Association of Veterinary Physiotherapists websites) and be aware they remain responsible for the animal under treatment.

Therapeutic exercises

Overwhelming evidence now exists in human beings that therapeutic exercise is not only useful, but necessary to manage chronic pain (Ambrose, 2015).

It has been suggested exercise maintains a normal secretion of endogenous opioids, thereby preventing central sensitisation due to the activation of NMDA receptors in the spinal cord (Sluka, 2013; **Figure 3**).

Figure 3. It has been suggested exercise maintains a normal secretion of endogenous opioids, thereby preventing central sensitisation.

Long-term immobilisation and/or reduced mobility also leads to joint ankylose, cartilage erosion, reduced tendon and ligament strength and muscular atrophy.

To be successful, an exercise regime must include some controlled aerobic exercise (lead walk, for instance) and some targeted exercises to improve strength and joint range of movement (Starr, 2013).

Hydrotherapy

Hydrotherapy is a form of therapeutic exercise using the properties of water to assist movement. Buoyancy reduces weight bearing, while viscosity increases muscle workload, allowing it to build up strength and stamina.

The hydrostatic pressure and warmth of the water may have additional benefits (such as muscle relaxation, increased blood flow and improved proprioception; Chiquoine, 2013).

Hydrotherapy centres usually offer either free/assisted swimming in a pool or walking in an underwater treadmill. These are two different types of therapeutic exercise with specific indications. The referring vet should check the qualifications of the hydrotherapist before referral to ascertain whether he or she is capable of looking after a patient's specific needs.

Unless the hydrotherapy centre is under veterinary supervision, the referring vet remains responsible for the patient during the hydrotherapy course.

Acupuncture

Acupuncture is an ancient art of healing from Chinese medicine. It relies on a holistic approach of the body as a whole integrated structure.

Acupuncture has peripheral and central effects. It can trigger the release of endorphins and encourage the endogenous healing mechanisms. In human medicine, several good quality, randomised control trials have demonstrated its effectiveness, particularly in pain management (Alvarez, 2015).

Therefore, it may be useful in long-term management of chronic pain, having little, if any, side effects. It may only be practised by vets with specific training in veterinary acupuncture.

Weight management

Managing obesity is an integral part of the management of chronic pain related to OA. Indeed, weight reduction alone has been demonstrated to reduce lameness scores in dogs with osteoarthritic pain (Smith, 2006; Marshall, 2010; Impellizeri, 2000).

It is also suspected increased adipocyte activity leads to a chronic low-grade inflammatory state, thereby worsening the symptoms of OA (Marshall, 2009; Fox and Mills, 2011).

How to prescribe a therapeutic plan

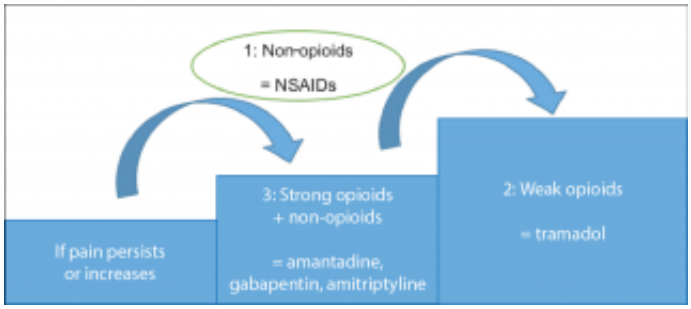

Figure 4. Analgesic ladder, adapted from the World Health Organization.

By analogy, with the guidelines of the World Health Organization's analgesic ladder in human medicine (**Figure 4**), the medical management of chronic pain should generally start with the prescription of an NSAID, which is also in accordance with the cascade.

Tramadol can then be added as needed, followed by a stronger opioid in case of acute or chronic pain. Paracetamol may be added at any step, with or without NSAIDs. Gabapentin, amantadine and amitriptyline may be used in cases of suspected neuropathic and/or centralised pain, with informed consent of the owner as these are unlicensed medications.

Non-medical management and nutraceuticals may be considered at any step, even (or especially) in the early stages, as preventive measures. When managing chronic pain, it is essential to remember no recipe will work for every patient. Each individual needs to be assessed thoroughly, to then be prescribed a treatment plan accordingly. Using pain scores as an outcome measure is useful to objectify the effect of the treatment.

Most cases will need some time to find the right treatment regime. This treatment will be regularly reviewed and modified according to the progress, changes in the disease and so on.

Overall, multimodal management is essential to tackle the different forms and consequences of chronic pain, to increase the chances of a successful outcome.

Acknowledgements

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- **Some drugs mentioned in this article are used under the cascade. Tables are for guidance only, and practitioners must always consult product SPCs for detailed information.**
- **This article was amended on 2/6/2016, at the author's request, to point out meloxicam is licensed for long-term use in cats in the UK.**

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