Chronic pain in small animals: how to create a pain management plan

Chronic pain impairs the quality of life of pets. Although the exact prevalence is unknown, recognition of chronic painful conditions has increased in the last few decades. Osteoarthritis may affect up to 20% of the canine adult population, although sources put this figure higher, at up to 40%. Chronic pain has a complex pathophysiology and a variety of presentations. The assessment can be challenging, as there may be several pathophysiological mechanisms underlying one disease. This clinical review gives an overview of chronic pain and demonstrates how to approach two case examples using the diagnostic tools available and illustrating the treatment options.

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Chronic pain is a common condition that has been recognised as affecting almost 20% of the human population worldwide (Breivik et al, 2006). Although the prevalence of chronically painful conditions in small animals is unknown, we can assume it is probably significant as a result of the increase in life expectancy. Chronic pain negatively influences the health and welfare of pets. The assessment of this condition has greatly improved over time as research has elucidated the pathophysiology of these diseases, and pain scoring scales and health-related quality of life instruments have been validated. However, the recognition and treatment of chronic pain is still considered limited (Robertson, 2008; Lorena et al, 2013). This clinical review presents how to approach two common chronic conditions (chronic intervertebral disc extrusion in dogs and osteoarthritis in cats), elucidating the pathophysiology of the pain presented, and explains the pain scoring systems available for the veterinarians with consideration given to different treatment options.

Chronic pain: an overview

Traditionally, pain was regarded as chronic when it lasted or recurred for more than 3–6 months (Merskey and Bogduk, 1994). This definition presents some limitations, as it does not take into account the variations in time between patients and conditions.

Chronic pain is currently defined as pain that persists past the normal healing time and hence has no protective purpose.

Sensitisation is a characteristic of chronic pain. It is a decrease in the threshold and an increase in the magnitude of the response to a noxious stimulus and can be peripheral or central, depending on the location. Repeated, prolonged and intense stimuli in the periphery may lead to central sensitisation through complex pathophysiological mechanisms.

Two characteristics of central sensitisation are hyperalgesia and allodynia. Hyperalgesia is defined as an increased response to a noxious stimulus, while allodynia is a response from a stimulus that is generally not regarded as painful.

The International Association for the Study of Pain (2021) recognises three main categories of pain: nociceptive, neuropathic and nociplastic:

- Nociceptive pain arises from actual or potential threat to non-neural tissue and is caused by the activation of nociceptors.
- Neuropathic pain is caused by a lesion or disease to the somatosensory nervous system and is further divided into central and peripheral, depending on the location of the injury. Nociceptive and neuropathic pain can co-exist
- Nociplastic pain arises from altered nociception, despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain.

Pain can be divided into three main components: the sensory, emotional and cognitive component. The sensory component is the simple sensation associated with pain and ceases once the stimulus is removed. The emotional component instead gives rise to the feeling of suffering, even in the absence of an actual nociceptive stimulus. The cognitive component is how the patient perceives the pain, the association made with the pain and the conditioned responses. When approaching animals with chronic pain, it

Table 1. Pain scoring scales validated for chronic pain in dogs

Scale	Validation
Canine Brief Pain Inventory	Osteoarthritis, appendicular bone cancer
Helsinski Chronic Pain Index	Osteoarthritis
Client-Specific Outcome Measure	Osteoarthritis
Liverpool Osteoarthritis in Dogs	Osteoarthritis of the elbow
Vetmetrica Health-Related Quality of Life	General use
From American Animal Hospital Association (2022)	

Table 2. Pain scoring scales validated for chronic pain in cats

Scale	Validation
Musculoskeletal Pain Screening Checklist	Osteoarthritis
Feline Musculoskeletal Pain Index	Osteoarthritis
Client-Specific Outcome Measures	Osteoarthritis
Montreal Instrument for Cat Arthritis Testing (for use by caretaker)	Osteoarthritis
Montreal Instrument for Cat Arthritis Testing (for use by veterinarian)	Osteoarthritis
From American Animal Hospital Association (2022)	

is helpful to assess these components separately and to think about which type of pain the animal is experiencing in order to decide the best treatment option. A number of inflammatory mediators play a role in acute and chronic pain.

Of interest is nerve growth factor, a mediator involved in the pathophysiology of peripheral and central sensitisation (Enomoto et al, 2019). Nerve growth factor is a useful example for explaining the development of both conditions. It is produced and released by peripheral tissues in response to tissue damage , such as in osteoarthritis. When nerve growth factor binds to the tropomyosin kinase A receptor (TrkA) expressed on the peripheral terminals of sensory nerve fibres, the nerve growth factor–TrkA complex is transported to the cell body of sensory neurons, located in the dorsal root ganglia. This modulates the expression of a variety of cell surface receptors and ion channels involved in nociception, which results in an increased excitability of primary afferent fibres (peripheral sensitisation). The activation of other pro-nociceptive transmitters may promote the removal of the magnesium block of the N-methyl-D-aspartate (NMDA) receptor, allowing cellular wind-up. Once wind-up has developed, it induces and potentiates a wide dynamic range of neuronal responses to each stimulus. The end result of the wind-up process is neuroplasticity, which is a change in neuronal structure with potential enhancement of signal transduction. Prolonged nociceptive transmission to the spinal cord causes release of neurotransmitters (substance P, calcitonin gene-related peptide, glutamate and adenosine 5'-triphosphate) and neuromodulators (prostaglandins and nitric oxide) at the level of the dorsal horn. Substance P and calcitonin gene-related peptide are also released peripherally, causing protein plasma extravasation and vasodilation and contributing to the phenomenon of neurogenic inflammation (Sluka et al, 1995). These processes increase the probability of peripheral and central sensitisation and of transmission through the dorsal horn synapse and then, via third-order neurons, to the sensory cortex in the brain (Woolf, 1996; Enomoto et al, 2019).

Chronic pain assessment

In the clinical setting, the sensory component is evaluated through a thorough physical examination that helps the clinician to localise the source of the pain. However, the response elicited can vary depending on the amount of force used by the clinician and on the animal's behaviour; a response to a painful palpation may not be obvious in stoic cats and dogs. In chronically painful conditions, changes are often subtle and slow, and stress could potentially mask symptoms when presenting to the veterinarian. The role of the owner is fundamental in chronic pain assessment. To evaluate the emotional component of pain and to understand how much the animal is suffering and how much the disease is influencing its quality of life, different pain scoring systems have been validated. *Tables 1* and *2* summarise the validated pain scoring system available for dogs and cats (American Animal Hospital Association, 2022). All these scoring systems are owner-based questionnaires except for the Montreal Instrument for Cat Arthritis Testing, which is for use by veterinarians.

Chronic intervertebral disc disease in dogs

A condition resulting in neuropathic pain in dogs is spinal cord and nerve roots compression caused by intervertebral disc disease (IVDD). There may also be nociceptive pain associated with this.

Presentation

Clinical signs include abnormal behaviour, reduced appetite and activity, biting lower limbs, whimpering and changing position at rest. The signs can be continuous or intermittent in nature.

Pathophysiology

The pathophysiology of neuropathic pain is complex and requires an initial intense nociceptive impulse (in this case, the disc protrusion) that does not decrease as healing occurs. This chronic stimulus leads to neuronal hyperexcitability (the so called 'ectopic afferent activity'), peripheral and central sensitisation, microglia activation and release of inflammatory mediators that are involved in the maintenance of the chronic pain state.

Assessment

A full orthopaedic and neurological examination should be performed initially to evaluate the sensory component of pain and to localise the injury. Once the diagnosis is confirmed, a pain consultation should involve the use of a pain scale in order to assess how much this condition is affecting the animal's quality of life. A helpful tool to assess the emotional component of the pain is the Vetmetrica Health-Related Quality of Life questionnaire (http://newmetrica.com). The questionnaire is web-based, easy and quick

to complete; it includes 22 questions that give a score for both the physical and emotional wellbeing of the dog. Once the questionnaire is completed, a graph will be generated. The results are compared with the results of average healthy dogs and so are easy to interpret. This questionnaire has to be repeated over time to assess progression/deterioration of the disease and efficacy of the treatment.

Therapeutic approach

Treatment is aimed at targeting the mechanisms underlying neuropathic pain. At present, the drugs recommended in veterinary medicine are mainly gabapentin and pregabalin. Tricyclic antidepressants are also suggested in few case reports (Cashmore et al, 2009; Plessas et al, 2012). Neuropathic pain is typically less responsive to non steroidal anti-inflammatory drugs (NSAIDs). However, in some cases of IVDD prostaglandins are induced by concurrent inflammation and so NSAIDs may be beneficial as they block the inflammatory effects of prostaglandins through inhibition of the breakdown of arachidonic acid by cyclo-oxygenase (COX). Meloxicam is an NSAID preferential cyclo-oxygenase 2 (COX-2) inhibitor, used for the treatment of osteoarthritis in dogs. Since an overexpression of COX-2 has been observed with peripheral neuropathic pain in humans (Durrenberger et al, 2006), meloxicam may be useful in treating this condition. However, one study failed to show any improvement in the Canine Brief Pain Inventory when meloxicam was combined with gabapentin, compared to the use of gabapentin alone (Ruel et al, 2020).

Gabapentin and pregabalin are structural analogues to the neurotransmitter gaba-amino butyric acid (GABA). The exact mechanism of action is not fully understood, although it is probably mediated through blockage of calcium channels on neurons, which results in a decreased release of excitatory neurotransmitters through the activation of spinal noradrenergic activity (Hayashida et al, 2007). Gabapentin is commonly used in the clinical setting to treat neuropathic pain, although the evidence for its use is limited. Two veterinary studies were unable to prove any benefit compared with placebo (Wagner et al, 2010; Aghighi et al, 2012). However, an inappropriate dose regimen and their use in the immediate postoperative period may have influenced these results. Pharmacokinetic studies suggest the use of 10–20 mg/kg every 8 hours orally in dogs, although sedation is seen at higher doses.

Pregabalin has a higher oral bioavailability and longer half-life and it is recommended at the dose of 2–4 mg/kg per os every 12 hours. In one study, pregabalin was proven to be effective in reducing postoperative pain in dogs following hemilaminectomy (Schmierer et al, 2020).

Amantadine is an NMDA antagonist that may reduce central sensitisation in dogs with chronic pain (Lascelles et al, 2008). It is used at 3–5 mg/kg per os every 24 hours. At the moment, studies supporting its use in dogs are limited (Lascelles et al, 2008; Madden et al, 2014).

Paracetamol's mechanism of action is traditionally reported as unknown and several studies report varying potential actions. Some studies demonstrate that the anti-pyretic (central COX inhibition) and analgesic mechanisms are reported to be separate and that capsaicin receptor TRPV1-mediated anti-nociception plays a pivotal role (Nilsson et al, 2021). Other potential mechanisms of action are on the opioidergic, cannabinoid and serotoninergic systems (Smith, 2009). There are currently no studies evaluating the efficacy of this drug in treating neuropathic pain in dogs, and the evidence for its use in this condition is limited in human medicine too.

Amytriptyline (a tricyclic anti-depressant commonly used in humans to treat neuropathic pain) inhibits the re-uptake of serotonine and noradrenaline and can be used at the dose of 1–2 mg/kg per os every 12 hours in dogs, although the evidence is scarce (*Table 3*).

Other strategies can be considered for the management of neuropathic pain. Higher bodyweight is one of the risk factors associated with canine osteoarthritis (Anderson et al, 2018), and a link between obesity and neuropathic pain has also been established in people (Hozumi et al, 2016). Therefore, weight management may be considered to treat this condition. Muscle relaxants (such as methocarbamol) can be used an adjunctive therapy to treat muscle spasms caused by IVDD. Low-level laser therapy has been used to treat different injuries in human. The mechanism behind its action is called photobiomodulation: laser therapy may reduce the inflammatory response and promote axonal regeneration following spinal cord injury (Byrnes et al, 2005). One research study showed how low-level laser therapy reduced time to ambulation in dogs undergoing hemilaminectomies (Draper et al, 2012).

Osteoarthritis in cats

Osteoarthritis has been clinically defined as a slowly evolving articular disease characterised by the gradual development of joint pain, stiffness and the limitation of motion (Bennett, 2010).

Table 3. Medications used to treat neuropathic pain in dogs

Drug	Dosage mg/kg per os	Mechanism of action	Frequency
Meloxicam	0.2 then 0.1	Cyclooxygenase-2 inhibitor	Every 24 hours
Gabapentin	5–10	Calcium channels blockers	Every 8 hours
Pregabalin	2–4	Calcium channels blockers	Every 12 hours
Amantadine	3–5	N-methyl-D-aspartate nantagonist	Every 12–24 hours
Paracetamol	10–25	Not fully understood, cyclooxygenase-1; cyclooxygenase-2 inhibitor, TRPV1 capsaicin receptor – antinociception	Every 8 hours
Amytriptyline	3–4	Serotonine re-uptake inhibitor	Every 12 hours

Presentation

Clinical signs in cats include reduced ability to jump, reduced activity, change in temperament and in the grooming habits (Slingerland et al, 2011). Lameness is not seen as commonly as in dogs as cats often have bilateral disease. Osteoarthritis can be primary (idiopathic) or secondary to pre-existing joint disease or trauma (less common). The radiographic presence of osteophytes is regarded as the key radiographic feature of osteoarthritis, although clinically affected cats may not present with them. While the prevalence of osteoarthritis in cats is unknown (Lascelles et al, 2010), 90% of cats above 12 years old have radiographic evidence of arthritic changes.

Pathophysiology

The pathophysiology is complex and involves inflammatory, biomechanical and metabolic components, resulting in degeneration of synovial joints. So far, the only risk factor associated with feline osteoarthritis is age (Slingerland et al, 2011).

Assessment

A cat presenting to a veterinarian with the aforementioned signs must undergo a full physical examination. Manipulation and palpation of the joints must be performed. Cats can be challenging to assess: it is not rare for cats to become aggressive and uncooperative so a full orthopaedic and neurological examination may often be difficult to obtain.

In order to understand how much the cat is suffering from the condition, the owner can be asked to complete the Feline Musculoskeletal Pain Index. The pain scale involves the owner assessment of the severity and impact of chronic pain on their cat, although its validation is ongoing. The most recent version consists of 17 questions regarding mobility, ability to perform daily activities and interaction with other pets and people. Each item can be scored from 'normal' to 'not at all'. The Feline Musculoskeletal Pain Index differentiates healthy cats from those with osetoarthritis, and helps to evaluate the response to treatment if repeated over time. The Feline Musculoskeletal Pain Index can be downloaded from the website of the North Carolina State University (www.cvm.ncsu.edu/research/labs/clinical-sciences/comparative-pain-research/clinical-metrology-instruments) and a short form is also available.

Therapeutic approach

There is enough evidence to support the use of NSAIDs in cats (Lascelles et al, 2001). However, the potential adverse effects of these compounds may prevent their use in older animals. Meloxicam, together with robenacoxib, is one of the two NSAIDs licenced for long-term use in cats in UK. It has proven to be very effective for treating chronic pain in arthritic cats (Lascelles et al, 2001; Lascelles et al, 2007a, 2007b; Bennett and Morton, 2009). If administered orally, meloxicam has a half-life of approximately 24 hours, allowing effective once-daily dosing (Lascelles et al, 2007b) with a bioavailability of 80%. The recommended dose of meloxicam is 0.1 mg/kg per os on the first day and then 0.05 mg/kg once a day. There is evidence to support administering lower doses, although this work was not supported by objective assessment such as pain scoring (Gunew et al, 2008). There is also no evidence that lower doses are safer in cases of renal disease. The same study suggested that actually meloxicam may indirectly improve renal function increasing the level of activity, water consumption and the stress level, as cats receiving meloxicam showed less increases in creatine over time compared to the control group (Gunew et al, 2008).

Feline-specific anti-nerve growth factor antibody is a promising therapy in management of chronic pain. Nerve growth factor contributes to peripheral and central sensitisation, and its concentrations are increased in chronic painful conditions including osteoarthritis. Frunevetmab (Solensia), which received marketing authorisation in 2021, is the first monoclonal antibody licenced for use in cats with osteoarthritis. Its pharmacokinetic profile is encouraging: it functions like naturally occurring antibodies, and is metabolised with minimal involvement of the liver or kidneys in their metabolism and elimination process, and minimal gastrointestinal impact. It is given monthly by subcutaneous injection. In a large multicentric study, 182 cats treated monthly with frunevetmab for 3 months showed significant improvement in the Client-Specific Outcome Measures questionnaire, the owner-assessed global treatment response and in veterinarian-assessed joint pain compared to a placebo. Side effects did not differ between control and placebo group, but skin disorders were more likely to occur in the treated group (Gruen et al, 2021).

Tramadol has a variety of mechanisms of action. It mainly binds mu-opioid receptors and it inhibits the reuptake of serotonin and noradrenaline. It has been shown to decrease central sensitisation and improve motor activity and the quality of life in cats with osteoarthritis (2–4 mg/kg per os every 12 hours, for 5–19 days) (Monteiro et al, 2016, 2017). In contrast to dogs, cats produce a high quantity of O-desmethyltramadol, metabolite associated with pharmacological effects (Kukanich, 2013). Although it seems to be safe and provide analgesia, oral tramadol is bitter, making it difficult to administer to some cats.

Gabapentin is another treatment option for managing osteoarthritis. Client-owned cats receiving gabapentin at the dose of 10 mg/kg every per os 12 hours for 2 weeks showed improved owner-identified impaired activities (Client-Specific Outcome Measures), but decreased motor activity, likely because of sedation (Guedes et al, 2018). Future work should examine the use of gabapentin at lower doses.

The evidence for using amitriptyline is very limited. It improved clinical signs in most cats with severe recurrent idiopathic cystitis (Chew et al, 1998). In other studies using 5 or 10 mg/day per os for 7 days, no efficacy was observed (Kraijer et al, 2003; Kruger et al, 2003). However the duration of treatment was short, especially considering that an analgesic trial of a minimum of 4 weeks is recommended in people.

Amantadine is anecdotally administered as an adjuvant to cats with chronic pain that are refractory to NSAIDs, although studies on its efficacy are lacking. In a study of 13 cats (Shipley et al, 2021), amantadine 5 mg/kg per os every 24 hours for 3 weeks improved the owner-identified impaired mobility (Client-Specific Outcome Measures) and the quality of life but decreased the locomotor activity when compared to placebo (*Table 4*).

Table 4. Medications used to treat osteoarthritis in cats

Drug	Dosage mg/kg, route	Mechanism of action	Frequency
Meloxicam	0.1, then 0.05 per os	Cyclo-oxygenase-2 inhibitor	Every 24 hours
Robenacoxib	1–2 per os	Cyclo-oxygenase-2 inhibitor	Every 24 hours
Frunevetmab	1–2.8 subcutaneous	Anti-nerve growth factor	Once a month
Tramadol	2–4 per os	Mu-receptors agonist, serotonin and noradrenaline re-uptake inhibitor	Every 12 hours
Gabapentin	10 per os	Calcium channel blocker	Every 12 hours
Amytriptyline	0.5–1 per os	Tricyclic antidepressant	Every 24 hours
Amantadine	1–4 per os	N-methyl-D-aspartate antagonist	Every 24 hours

Conclusions

Chronic pain can be present in a variety of conditions and can persist as a disease itself. Although diagnosis is challenging and not always possible, health-related questionnaires are now validated and can be used to assess the level of pain an animal is experiencing and the response to treatment over time. The evidence for some of the therapeutic options is still very limited; further studies are required to investigate their efficacy and we must pay close attention to evaluating the analgesic benefits of all available treatments. CA

Further reading

Please see www.zeropainphilosophy.com for further information.

Conflicts of interest

The authors declare no conflicts of interest.

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KEY POINTS

- Chronic pain affects animals' quality of life.
- Pathophysiology is complex and involves different inflammatory mediators.
- The same underlying disease can present with a variety of clinical signs.
- Health-related quality of life questionnaires are now validated and are a fundamental tool in chronic pain consultations.
- Treatment options are available, but the evidence for the use of some of them is lacking.

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