CPD article

# Understanding the pharmaceutical approach to pain management in canine osteoarthritis

Canine osteoarthritis was recently reclassified as a welfare concern by the Veterinary Companion Animal Surveillance System (VetCompass), an initiative run by the Royal College of Veterinary Surgeons, focused on improving companion animal health. This condition is a common cause for consultation in first opinion practice, with an estimated 35% of the canine population being affected. Chronic pain is complex and a multimodal approach is best for management, which includes pharmaceuticals employed in a methodical manner. This article provides an overview of the types of pain associated with canine osteoarthritis, as well as how to recognise them. Making reference to hypothetical cases, the appropriate pharmaceutical management is described. Further management strategies, as part of a multimodal approach, are summarised to ensure best practice.

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**Hannah Capon,** Director, Canine Arthritis Management, 68 Middle Road, Brighton, BN43 6GA, UK, hannah@caninearthritis.co.uk

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Canine osteoarthritis, estimated to affect 35% of the canine population (Muller et al, 2018), is a leading cause of chronic pain, which is often more appropriately termed maladaptive pain. While chronic pain is likely to be of long duration, that is not likely to be its sole feature. Chronic pain is a complex pathophysiological experience, differing from acute pain, that affects the whole body through inducing a sustained catabolic state, as well as having a negative impact on cognitive and emotional health long-term (Woolf, 2004; Self and Grubb, 2019).

## Chronic pain associated with canine osteoarthritis

### Persistent nociceptive pain

Acute nociceptive pain has physiological benefit, as it signals potential or actual tissue damage caused by stimuli such as heat, cold, pressure or chemicals. It protects through causing appropriate action to be taken by the dog to avoid harm and encourages behaviours that support healing. Although this pain is adaptive, it still needs addressing with a comprehensive, prompt, targeted pain management approach.

### Persistent inflammatory nociceptive pain

Inflammatory mediators from tissue damage in and around arthritic joints create an 'inflammatory soup'. This lowers the threshold and promotes the firing of active nociceptors, which recruit inactive, previously high-threshold nociceptors and encourages spontaneous action potentials. This is peripheral sensitisation which is identifiable as hyperalgesia, where a noxious stimulus that previously resulted in only mild pain now results in significant pain.

### Central sensitisation related pain

This is a complex neuro-plastic derangement, involving decreased central descending inhibition, facilitated ascending nociceptive transmission and promotion of non-nociceptive stimuli as nociceptive, as a result of the failure of inhibitory neurons within the dorsal horn. This is a consequence of constant nociceptive stimulation. This pathophysiological change is identifiable as allodynia, where normal innocuous stimuli are perceived as pain. The pain of osteoarthritis becomes independent of the disease within the joint and needs to be considered as an associated disease, which requires a concurrent approach. The progression to central sensitisation is not predictable and each dog must be assessed on an individual basis while considering this possibility.

### Neuropathic pain

Actual damage of the peripheral or central nervous system. This may occur through localised nerve involvement or may

be associated with concurrent radiculopathy or spinal cord compression caused by disc disease.

Please note the difference between neuropathic and neurogenic pain. Neuropathic pain is caused by a lesion or disease of the somatosensory nervous system. Neurogenic pain is a result of nervous system plasticity, caused by constant stimulation as seen in inflammatory pain and central sensitisation.

Other sources of pain often not considered when managing osteoarthritis associated pain states include:

- Within nociceptive and inflammatory nociceptive, there is pain associated with compromised soft tissue. This is called myofascial pain and it is commonly associated with the inappropriate use of muscles as a result of adapted postures and gait
- Referred pain, caused by confusion of the locality of the ascending stimulus at the dorsal horn of the spinal cord.
- Post-operative pain believed to be (or be 'likely to be') caused by maladaptive tissue healing, which may be associated with surgeries (Fox, 2016; Hunt and White, 2019).

Maladaptive pain associated with osteoarthritis is complex, ever-remodelling and clinically challenging to manage. A clinician must be attentive to the dog's pain picture and understand the neuropathophysiology, in order to target the inevitable changing pain state throughout the course of the disease.

Studies of osteoarthritis suggest that between 5.4% and 15.2% of affected dogs have associated maladaptive pain. To the best of the author's knowledge, accurate assessment of concomitant neuropathic and persistent nociceptive pain in the osteoarthritis-afflicted canine population has not been researched to date (Dimitroulas et al, 2014).

## How to identify the different pain types associated with canine osteoarthritis

Identifying the 'type' of pain requiring management will enable an appropriate choice of analgesia. Inflammatory nociception is always present in osteoarthritis. Indicators of pain and pathology will be localised to the compromised joint. The dog will appear to be their normal self and will tolerate palpation everywhere except for the joint(s) of concern. The affected joint may feel warm and potentially effused or swollen and manipulation of the joint may cause a withdrawal response or another strong reaction.

A dog exhibiting central sensitisation is likely to behave in a manner that far exceeds what is expected of the pathology presented. The history may suggest a change in behaviour, such as being less social with the family, being less tolerant of other dogs, or becoming more unpredictable. The dog may be more averse to handling of the affected joint and the surrounding locality and may potentially be reactive to local touch or even the possibility of touch (allodynia).

Please note, the stress of the consulting room environment may influence a dog's ability to express discomfort. The dog may appear stoic and show only subtle signs of discomfort such as sidestepping during examination and being wide-eyed or using their peripheral vision as they anxiously monitor your every move.

Neuropathic pain is commonly identified as a result of the owner's observations of their dog and is associated with spontaneous pain, strange sensations such as pins and needles, or burning sensations (dysthesia). Sudden onset of abnormal behaviours such as frantic nibbling and chewing, persistent licking of specific locations, or turning suddenly or running away as if just bitten, may indicate the presence of neuropathic pain.

Myofascial pain is identified through postural and physical changes such as abnormal coat patterns and recognition of subtle local twitch reflexes on appropriate palpation of the soft tissues (Hielm-Bjorkman, 2014; Epstein et al, 2015; Belshaw and Yeates, 2018; Mills et al, 2020). The clinician must collate the dog's history, conduct/perform a systemic health assessment, examine the joints and location(s) of concern and consider the signalment, in order to create a differential list and identify the pain types and severity.

It is important to remember that canine osteoarthritis is generally secondary to another underlying joint disease (Anderson et al, 2018). Considering breed predisposition will ensure an appropriate investigation and allow all treatment options to be considered.

A common mistake (while performing examination of a dog with suspected osteoarthritis) is feeling pressured to either fix everything at once, or the opposite - prescribing one medication to fix everything. Neither approach is appropriate and instead the clinician should aim to:

1. Clinically reason the dog's pain state, then consider the pharmaceuticals required
2. Manage owner expectations by suggesting that pain is complex, that a tailored approach is required and no 'one size fits all' strategy exists
3. Explain that pain management plans need to be routinely reviewed initially every 2–4 weeks
4. Encourage owner-led objective monitoring using clinical metrology instruments or client specific outcome measures and use these alongside full clinical examination at each review (Hunt and White, 2019).

## Fictitious cases and clinically reasoned pharmaceutical approaches

With the hope of adding context, commonly employed pharmaceuticals will be explored through the presentation of three case studies.

Please note that in these fictitious cases, the owners have refused further diagnostic imaging investigations and a conservative approach is the only option. This is not ideal and the pursuit of an accurate diagnosis should always be promoted. However, it is common in first opinion practice to work with only clinical examination and reasoning, without diagnostics. We must bear in mind that there are currently no objective measures, including imaging, that can predict the presence or the severity of pain. The clinician must use diagnostics to rule out differentials, not to assess severity.

The author suggests that the importance of imaging is conveyed to the owner. A rational compromise may involve insisting on further investigations, if an inadequate response is seen to a clinically reasoned approach.

## Case 1

- 11-year-old male neutered chocolate Labrador, body condition score (BCS) 6/9, with thick neck and 'mane' and flat splayed forepaw digits
- Enthusiastic greeting and wagging tail, but uncoordinated stiff gait and little movement through the back. The dog was keen for attention and not averse to being palpated all over
- The owner reports the dog as being is bright and as enthusiastic as always, but stiff and exercise-intolerant. The stiffness improved during the walks, but afterwards the dog once again appears uncomfortable
- Reduced range of motion and crepitus in carpi, elbows, shoulders, hocks, stifles back and hips were observed. No significant effusion or joint instability was detected.

Provisional diagnosis was bilateral carpal, elbow, shoulder, hock, stifle and hip osteoarthritis and multilocality spondylosis. In this case, the lack of demeanour changes and clinical signs correlate well with the identified pathology. Targeting persistent inflammatory nociceptive pain is an appropriate plan.

Canine osteoarthritis is a localised inflammatory disease mediated by cytokines, chemokines, prostanoids, proteolytic enzymes and nerve and vascular growth factors. (Dimitroulas et al, 2014) There is an upregulation of COX-2 within the diseased joint, leading to prostaglandin synthesis and peripheral nociceptor sensitisation. Normal movement and loading that previously did not exceed peripheral nociceptor thresholds within joint structures now transduce action potentials, signalling to the central nervous system that noxious stimuli is occurring.

Initiating a pharmaceutical approach with a cyclo-oxygenase-2 (COX-2) selective non-steroidal anti-inflammatory (NSAID) or piprant is appropriate (Hunt and White, 2019).

### Key considerations:

- NSAIDs are known to produce a peripheral anti-inflammatory effect, as well as influencing sensitisation of the central nervous system (Burian and Geisslinger, 2005)
- Currently no COX-2 selective NSAID is considered superior in efficacy or safety to any other NSAID.
- Potential adverse events are gastrointestinal problems, renal insufficiency, anorexia, lethargy and death. Gastrointestinal signs are most likely (Lawson and Walton, 2019) and greater COX-2 selectivity are more likely to be tolerated (Hunt and White, 2019). It is also important to consider owner compliance factors.
- Poor response to one NSAID should be followed by a wash-out period of between 24 hours and 7 days (depending on practitioner), and introduction to another NSAID (Hunt and White, 2019).
- A true hepatotoxic adverse reaction to an NSAID is likely to occur early in the course (Kukanich et al, 2012; Lawson and Walton, 2019). Long-term NSAID reliance doesn't correlate with increased likelihood of adverse events (Innes et al, 2010). Manage owner's fears early by clarifying that gastrointestinal related adverse events do occur but are generally self-limiting. If signs occur, advise owners to cease dosing immediately and contact the practice.
- An adverse reaction to one NSAID does not rule out the possibility of successful use of another NSAID. Allow a gastrointestinal healing time of 5–14 days (depending on practitioner) and introduce another NSAID (Kukanich et al, 2012). The author will trial up to 3 or 4 (depending on the client), before accepting that NSAIDs are not suitable.
- Comorbidities being confused as adverse reactions can be avoided with early biochemistry and haematology surveillance, which should be encouraged once or twice a year (Lawson and Walton, 2019).
- NSAIDs have improved efficacy with time, because the underlying inflammation of osteoarthritis is persistent and is best treated continuously. Dispensing protocols should convey confidence and the potential for an initial course of 12 weeks or longer. (Innes et al, 2010)
- Piprants act further down the inflammatory cascade, targeting the E-type prostaglandin receptor 4. They are not associated with prostaglandin related side effects. Transient vomiting may occur, which should not influence the dosing regimen if there are no systemic consequences (Rausch-Derra et al, 2016). The low side effect profile means they are an appropriate first line medication, especially in dogs that may be reliant on anti-inflammatory intervention for life (Rausch-Derra et al, 2015).
- Through instigating a multimodal approach alongside NSAID prescription, there is increased likelihood that reliance on an NSAID may decrease or in some cases even cease.

### Other key points for owner education:

- The importance of weight loss and support in reaching a target BCS of 4.5/9 (Smith et al, 2006)
- A holistic approach to managing pain, mobility and safety with attention being paid to foot care and claw length.
- An explanation of the benefits of complementary or integrative therapies, such as hydrotherapy, which will aid weight loss and develop strength and stamina, as well as assisting a return to functional movement (Preston and Wills, 2018; Bockstahler et al, 2019), which may reduce reliance on NSAIDs.
- Every effort needs to be made to ensure referrals for integrative therapies are with well-qualified, suitably insured and experienced professionals. Communication channels must remain open to ensure best practice.
- Education regarding the intermittent inflammatory flare-up nature of osteoarthritis and the additional pharmaceuticals that may be required to manage these (Belshaw et al, 2020).

## Case 2

- 8-month-old female entire Golden Retriever with BCS of 4/9.
- The dog is very exuberant, will not stand still and avoids sitting down. She has a dramatic waistline wiggle.
- The owner suggests she has been difficult to train, tires easily on walks, loves playing ball but lies down intermittently. The owner notes only a few bouts of transient hindlimb lameness and is unsure whether there is a problem or how far it may have progressed.
- The dog is a real handful to examine, especially around her hips, showing avoidance strategies to handling. There is

restricted range of motion and withdrawal in both hips, as well as an acute pain response on palpation of the glutaeal muscles and pectineus. No subluxation is palpated.

The provisional diagnosis is early osteoarthritis secondary to bilateral hip dysplasia with associated myalgia. In this case, there are changes in the dog's demeanour, as well as behavioural responses, which suggest greater perceived pain or potential pain, from a larger field of tissue than the actual pathology. This is a result of convergence and central sensitisation at the dorsal horn of the neurons processing the nociceptive stimuli from the joint with other inputs, such as Aβ mechanosensitive afferents from surrounding tissue. Normally signalling touch and vibration, these afferents from the surrounding locality now evoke pain.

The myalgia associated with the joint pathology is subsequent to muscle tension and spasms maintained through spinal reflexes. A reflex response to restrict joint movement.

Initiating a pharmaceutical approach with a (COX-2) selective NSAID or piprant with a concern of hyperalgesia and allodynia is appropriate. In this case, little improvement was seen after 4 weeks of NSAID use.

### Key considerations:

- Inadequate improvement on a long trial of NSAIDs alone welcomes the addition of an N-methyl-D-aspartate (NMDA) receptor antagonist such as amantadine (not licenced) or memantine (not licenced), which reduce the spontaneous and low threshold firing of the postsynaptic neurons in the dorsal horn that contribute to central sensitisation (Lascelles et al, 2008; Walton et al, 2013)
- Amantadine can be prohibitively expensive, which explains the interest in using memantine.
- Amantadine and memantine may be more effective if given twice daily as opposed to once daily (Pozzi et al, 2006; Schneider et al, 2009)
- N-Methyl-D-aspartic acid (NDMA) receptor antagonists may take 3–4 weeks to demonstrate effectiveness (Lascelles et al, 2008). Reassessing the effect at 4 weeks and taking further action as appropriate is advised
- Adverse events are rare but include self-limiting agitation, sedation and gastrointestinal signs (KuKanich, 2013).
- Amantadine and memantine are excreted by the kidney so monitoring bloods and urine is wise and the dose may need to be adjusted as required.

### Other key points for owner education:

- Hot and cold therapy can be beneficial (Bockstahler et al, 2019)
- The importance of controlled regular exercise to reduce aggravating the inflamed joints and associated myalgia
- Minimise deterioration caused by induced acute flares and associated soft tissue damage caused by accidents and repetitive stress injuries in an unsuitable home environment. For example, discourage uncontrolled use of stairs and jumping on and off furniture
- Hydrotherapy may expedite improvement and successful management of this lifelong condition, but initial pain control is essential
- Other modalities such as transcutaneous electrical nerve stimulation, laser or acupuncture may be considered (Bockstahler et al, 2019)
- Advise that resolving the pain will not create a compliant/obedient dog. Further training and behaviour modification will be required
- Suggest further diagnostics and contacting the breeder, as well as registration on the Canine Health Scheme
- Education regarding the intermittent inflammatory flare nature of osteoarthritis and the possibility of using paracetamol at the licensed dose (Gurney and Bradbrook, 2020).

## Case 3

- 9-year-old male neutered German Shepherd with a BCS of 5/9. The dog presents with significant mane, weak, sloped and unstable poorly muscled hindlimbs and visibly irregularly worn claws
- His attempts to correct poor limb placement are diminished and the hind feet can be heard dragging intermittently. Intermittent forelimb lameness noted, the dog has difficulty getting to a stand-from-seated position and easily slips and falls
- Owner reports he is not himself, incessantly licks his medial forelimbs and has become reactive and unpredictable around people and dogs. He has bitten someone, he pants and paces at night and does not settle well. When he does lie down, he may kick out with a hind limb occasionally
- He has a significantly reduced range of motion in bilateral elbows with palpable remodelling and is acutely reactive when attempts are made to palpate grossly thickened stifles.

The provisional diagnosis is that multi-locality osteoarthritis is likely, based on clinical observations and breed predilection. The possibility of central and peripheral nervous system pathology such as intervertebral disc disease and lumbosacral disease should not be overlooked.

In this case, there are profound changes in demeanour, as well as unpredictable behaviours, suggesting neuropathic pain symptoms, such as dysesthesia. Neuropathic pain, in the form of injury or trauma to the nerves, induces spontaneous ectopic foci in peripheral afferents and significant changes in central neuronal processing, disrupting the complex stimulus-specific sensory experiences normally carried by the somatosensory system.

Neurogenic pain from central sensitisation as a result of persistent nociceptive signalling culminates in facilitation of nociceptive messaging as well as innocuous stimulus, such as Aβ touch afferents, being projected to the higher centres as nociceptive pain, with a resultant allodynic state.

A pharmacological approach to this case requires promptly using adjuncts targeting central sensitisation, neuropathic pain and the affective component of pain, alongside the accepted first line approach with a (COX-2) selective NSAID or piprant.

The recent release of the monoclonal antibody, bedinvetmab (Librela or Zoetis) is likely to influence our approach to these cases through its action on nerve growth factor, which is a key player in neurogenic inflammation.

### Key considerations

- Gabapentin (not licenced) is an appropriate first line intervention. Start at a low dose and titrate up, until effect is noted, to avoid the common adverse events of lethargy and a weak/wobbly gait (Grubb, 2010). The adverse events seen are often worse in progressed cases that have muscle mass loss and paresis
- Gabapentin has a slow onset of effect, potentially 3–4 weeks (Grubb, 2010). Routine reassessment along this time interval and titrating to effect, through repeated dose and dosing frequency alterations, is advised in order to tailor the pharmaceutical approach to clinical response.
- Gabapentin has been noted to be an anxiolytic, a common concurrent concern in chronic pain cases. Varied doses, preferably three times daily, may lead to a reduction in night-time pacing.
- Do not simply stop the medication after moderate term use, otherwise there is a risk of rebound hyperalgesia. It is better to wean off over a few weeks (Grubb, 2010).
- Gabapentin may be best prescribed at a lower dose three times daily for a more continuous effect (KuKanich and Cohen, 2011).
- Gabapentin is not reliant on liver metabolism but doses should be moderated if the liver's metabolic function is in doubt. It is excreted by the kidneys, so it is important to perform a blood panel before use and adjust dose accordingly.
- Gabapentin is schedule 3, which means it can only be dispensed in a controlled manner. A vet can only prescribe 28 days of gabapentin at any one time (The Royal College of Veterinary Surgeons, 2017).
- Pregabalin (not licenced) has a quick and predictable absorption and action, with greater affinity for its receptor, which may equate to longer and more predictable duration of action. Dosing may only be required twice a day, but this can be increased to three times daily and the doses titrated if required (Salazar et al, 2009).
- Refer to the above regarding N-methyl-D-aspartate receptor antagonist use for action on central sensitisation. This may be required to replace gabapentin or pregabalin if either are ineffective at controlling central sensitisation, or if additional pain control is required. Addition is generally dependent on reaction to previously added adjuncts.
- Amitriptyline (not licenced) is a tricyclic antidepressant that is used to manage neuropathic and chronic pain, especially when emotional well-being is impacted. This may be added but must not be used in conjunction with tramadol, monoamine oxidases or other tricyclic antidepressants owing to the risk of serotonin syndrome (Grubb, 2010).
- Owners' expectations must be managed, with amitriptyline potentially taking 4–6 weeks to show effect (Rossmeisl and Moore, 2016).
- Tramadol is a schedule 3 synthetic opioid with additional effects through adrenergic and serotonergic receptors. It can only be dispensed in a controlled manner, for 28 days at any one time (The Royal College of Veterinary Surgeons, 2017).
- Its efficacy is unpredictable in dogs because of the variable metabolism into its active metabolite. However, it does appear to benefit some dogs so it should be considered (Kukanich and Papich, 2004; KuKanich, 2013).
- Tramadol may offer benefits towards emotional well-being and targeted dosing may aid disturbed sleep, as a reported adverse effect is mild sedation.

### Other key points for owner education:

- All osteoarthritis cases are prone to acute flare-ups and are commonly triggered by inappropriate activity or by falls or accidents. Accidents and exercise-induced stress must be minimised. Paracetamol can be used in addition to other medications for the period of an acute flare (Gurney and Bradbrook, 2020)
- Night pacing could be a clinical indicator of canine cognitive dysfunction (Fast et al, 2013), but this is an exclusion diagnosis. Excellent pain control is necessary before this diagnosis is made, as chronic pain can also have an impact on cognitive and emotional health, leading to disturbed sleep, confusion, and anxiety
- Behaviour changes and unpredictability may be observed as a consequence of the dog's attempts to avoid pain. It is so important to give the dog sufficient space and educate family members and guests to do the same, as well as suggesting seeking advice from a behaviourist
- Supported exercise with a caudal support harness has been suggested, but owners should be sympathetic to potential regional allodynia. Safe mobility in and out of the house should be ensured. Short walks of 5 minutes should be taken multiple times throughout the day, to avoid soft tissue fatigue
- It is worth also noting that this a long-term project and the improvement will be slow.

## Conclusions

Reviewing pharmaceutical approaches to pain management via case studies highlights its complexity. There is no 'cookie cutter' approach and excellent objective observation skills, as well as regular communication between stakeholders, is imperative to ensure the case is frequently reassessed, clinical improvement is seen and interventions are modified as the disease progresses.

Treatment options for chronic pain are complex and response to treatment is subject to much individual variation. The veterinarian must monitor health status effectively on an ongoing basis in order to tailor treatment to the individual.

Medical management of chronic pain is a dynamic and expanding field, with new products regularly coming onto the market. Monoclonal antibodies directed at nerve growth factor are an exciting prospect for managing peripheral and central sensitisation (Lascelles et al, 2015).

An often-overlooked medical intervention that is not commonly used is in-hospital interventions, such as constant rate infusions and parenteral analgesics. In the author's opinion and experience, these approaches may not be preferable as a result of the associated costs and inconvenience to both owners and veterinary practices. However, these potential interventions can be considered as a result of the improved safety, efficacy and rapid influence. Owner compliance factors should also be considered, especially because we underestimate the stress an owner endures while waiting for new medications to take effect.

Considering interventions that can expedite that transition should not be discounted.

### Conflicts of interest

The author declares no conflicts of interest.

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