# What can we learn from osteoarthritis pain in companion animals?

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*Received and accepted on September 4, 2017.*

*Clin Exp Rheumatol 2017; 35 (Suppl. 107): S53-S58.*



**Key words**: osteoarthritis, pain, canine, companion animal, animal model

*Competing interests: none declared.*

**ABSTRACT**

*The lack of successful translation of basic research discoveries into safe and effective treatments for chronic pain patients has led to increased scrutiny of the preclinical models used in pain research, particularly for osteoarthritis, where there is a significant disconnect between the animal models used to study the structural versus symptomatic aspects of the disease. Companion dogs offer a unique opportunity to assess osteoarthritis pain in a physiologically relevant 'model' of the disease. Approximately 20% of the canine pet population spontaneously develops osteoarthritis, translating to at least 15 million dogs in the United States alone. As in humans, pathogenesis of canine osteoarthritis involves changes in all tissues of the synovial joint including articular cartilage, subchondral bone, and periosteum. The dominant symptom of osteoarthritis for both humans and dogs is pain, and the current therapeutic goal for both species is management of that pain and associated loss of function. To capture clinically and translationally relevant pain severity and pain impact data in the companion canine osteoarthritis 'model', clinical metrology instruments have been validated. These instruments, which assess changes in spontaneous pain-related behaviours, over extended periods of time, in the dog's home environment, are used to evaluate the efficacy of novel interventions for chronic pain in canine osteoarthritis studies. There is evidence that these results in companion dogs can reliably predict efficacy in humans. Across many classes of compounds in which there have been studies in companion animal chronic pain conditions and the same conditions in humans, the analogous results have been seen. In addition, many of the drugs used to treat pain in people are successfully used off-label to treat pain in dogs as well. If preliminary indications of predictability hold true, companion dogs may be embraced as a missing link in the translation of osteoarthritis treatment from mice to men.*

Numerous reviews highlight the lack of successful translation of basic research discoveries into safe and effective treatments for chronic pain patients (1-10). The elucidation of the many signal-transduction pathways that contribute to peripheral and central sensitisation has led to a growing number of potential targets for 'first in class' drug development. However, over 90% of the launches of analgesics over the past 15 years were reformulations of existing pharmaceuticals (10). Thus, very few drugs with novel modes of action have been added to the therapeutic arsenal for the management of chronic pain patients. In addition, there have been several notable late-stage failures in translational pain research, where pre-clinical work in rodent models suggested compounds would be highly efficacious, yet clinical efficacy or safety was disappointing (12-14). The late-stage failures in particular, have led to increased scrutiny of the preclinical models used in pain research, particularly for osteoarthritis, where there is a significant disconnect between the animal models used to study the structural *versus* symptomatic aspects of the disease (15).

A review of animal models of osteoarthritis reveal over 20 different induction methods in 10 different species (6), including spontaneous models in aging animals such as mice and guinea pigs; genetically modified mice; as well as surgically, enzymatically, or chemically induced models in mice, rats, and dogs. No consensus currently exists regarding which model is most relevant to human osteoarthritis (15, 17). While the spontaneous models best mimic the slow progression of human disease with pathology and pathogenesis most

similar to those occurring in human osteoarthritis, they are expensive and time-consuming to use. As such, acute and severe chemically induced models are commonly used for the study of chronic osteoarthritis pain (15, 18-20). However, the initiating event and many of the pathological changes in these chemically induced models are not typical of human osteoarthritis (15, 21). As such acute models are suboptimal for studying chronic symptoms, it would be ideal to assess osteoarthritis pain in physiologically relevant models of chronic osteoarthritis (15). Companion animals offer a unique opportunity to do just that.

Osteoarthritis is common in companion animals such as dogs, cats and horses. Approximately 20% of the canine pet population over 1 year of age in the United States spontaneously develops OA, translating to at least 15 million dogs in the US alone. Up to 93% of all cats have radiographic signs of osteoarthritis, and approximately half have clinical signs associated with the disease (22-24). In horses, the inability to compete is due primarily to osteoarthritis, and lameness due to joint problems is the most common reason for euthanasia (25, 26). In many cases the osteoarthritis in companion animals is microscopically, macroscopically, physiologically, and symptomatically analogous to the human condition (27-39). This is particularly true in the case of the dog.

As in humans, the pathogenesis of canine osteoarthritis involves changes in all tissues of the synovial joint (40-47). Within the articular cartilage, imbalances exist between anabolic and catabolic processes. In the short term, there is an increase in cartilage thickness associated with increased cellularity, as well as extracellular matrix. Over time, there is degeneration with progressive loss of structure. The tissue loses compressive stiffness and tensile strength, and grossly, the cartilage surface begins to fibrillate. In the advanced stages, cartilage tissue is lost and erosion and ulceration develop. While it is unclear whether the processes are independent, the changes in articular cartilage are closely associated with changes in subchondral bone metabolism and architecture. The subchondral bone initially thins and increases in porosity with subsequent sclerosis of the subchondral bone plate. The subchondral bone sclerosis, along with osteophyte formation are key features of both human and canine osteoarthritis. The osteophytes form in the periosteum overlying the bone at the junction between the cartilage and bone. The osteophytes not only contribute to the functional properties of the affected joint, but also to the clinical symptoms in both species.

The dominant symptom of osteoarthritis for both humans and dogs is pain, and the current therapeutic goal for both species is management of that pain and associated loss of function. In both species, the pain is managed by a variety of approaches that include lifestyle changes (*e.g.,* exercise restriction, weight loss), systemic analgesics and anti-inflammatories, intra-articular injections, and rehabilitation. In some cases the osteoarthritis pain remains intractable and, in people, joint replacement becomes necessary. Joint replacement can also be an option in dogs with severe symptomatic osteoarthritis of the coxofemoral joints, however many owners opt for euthanasia for their dog if the pain and associated dysfunction becomes unmanageable. There is clearly great need for additional options for improved symptomatic treatment of osteoarthritis in both species. The fact that both the clinical symptomatology and osteoarthritis disease physiology is the same for both species, makes the companion dog an ideal 'model' to study both pain control and disease modification, as well as the relationship between the two.

Critical to being able to study the efficacy of novel interventions in companion dogs, is the use of valid and reliable outcome measures in appropriately designed and powered studies. Outcome assessment in pre-clinical models of osteoarthritis pain has received increased scrutiny in light of the failure of many models to reliably predict clinical effectiveness. Reflex withdrawal responses, such as tail flick or paw withdrawal, to sensory stimuli, such as von Frey or hot plate, have been the primary assessment methods of efficacy in animal models of pain. These reflex tests used to evaluate novel analgesic interventions are based on hyperactive reflexes. While evoked pain can be a problem for some people with osteoarthritis, spontaneous pain that occurs independent of a specific activity is the primary complaint of most patients (48). To account for the fact that pain is ultimately experienced as a culmination of complex information from the periphery, there has been a call to use outcomes that measure spontaneous behaviours as opposed to evoked responses (49), which has led to renewed interest in using operant assays in preclinical pain models. Operant systems utilise a reward-conflict platform, in which animals choose between receiving a reward or escaping an unpleasant stimulus. The animals control the amount of nociceptive stimulation and modify their behaviour based on cerebral processing. Measurement of these more complex, ethologically relevant behaviours is uncommonly employed in preclinical pain research, likely due to the increased time and costs of assay development and animal training that is required (50-52). For studies in companion dogs with osteoarthritis, there have been recent significant efforts to validate a variety of behaviour based, outcome assessment instruments that capture the intensity of spontaneous pain and its impact on the dog's activities of daily living.

Historically, studies designed to test the efficacy of interventions intended to decrease chronic pain in companion dogs with osteoarthritis have relied heavily on the assessment of lameness through the use of force plate gait analysis (53-59). While gait analysis is a gold standard measurement for lameness, it has the downsides of being extremely time consuming, requiring specialised equipment, and relies on relatively strict inclusion criteria. In addition, gait analysis only evaluates a dog at one specific point in time, and weight bearing on an affected limb is only one part of the much larger picture of chronic pain in dogs with osteoarthritis. Recently, as patient-oriented outcome measures have become a focus for both human and veterinary medicine, there has been a movement to the validation of more

'clinically relevant' outcome measures, which are now required for regulatory approval of drugs labelled for the treatment of pain in dogs with osteoarthritis. In order to capture changes in spontaneous pain-related behaviours, over extended periods of time, in the dog's home environment, outcome measures that can reliably quantify the owners' behaviour-based assessment of chronic pain in their pets have been developed (60). These measures, sometimes called 'clinical metrology instruments' are utilised by owners much the same way that parents or caregivers provide the proxy assessment of pain behaviours in young children or cognitively impaired individuals (61-64). These assessments allow the measurement of pain severity and its impact on the dog's function. In the case of the Canine Brief Pain Inventory (Fig. 1), the measure was developed specifically to not only reliably quantify chronic pain behaviours in dogs, but also to have translational relevance to human studies (65).

In order to capture clinically and translationally relevant pain severity and pain impact data in the companion canine osteoarthritis 'model', the Canine Brief Pain Inventory was developed to be directly analogous to the Brief Pain Inventory (BPI), which is a measure used to capture the severity of pain and its impact on daily living in people (66, 67). Designed using the standard methods for the development and psychometric testing of instruments designed to assess subjective states such as pain, the Canine BPI is an owner completed questionnaire that has the same factor format, question structure, and response scaling as the BPI. A Pain Severity Score (PSS) is generated through the average of 4 questions that are identical to those in the BPI, and a Pain Interference Score (PIS) is generated through the average of 6 questions, 3 of which are identical to those in the BPI. The Canine BPI has been validated in dogs with osteoarthritis as well as dogs with bone cancer 65, 68). While the Canine BPI is currently used as a primary outcome measure in registration studies for canine osteoarthritis pain, the ability of Canine BPI results to predict the outcome of analogous human clinical trials

**Today's Date:** ☐☐ / ☐☐ / ☐☐ (Month / Day / Year) **Patient/Study ID#** _____

***Canine Brief Pain Inventory (Canine BPI)***

**Description of Pain:**

Rate your dog's pain.

1. Fill in the oval next to the one number that best describes the pain at its **worst** in the last 7 days.
   ○0 ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10
   No Pain — Extreme Pain
2. Fill in the oval next to the one number that best describes the pain at its **least** in the last 7 days.
   ○0 ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10
   No Pain — Extreme Pain
3. Fill in the oval next to the one number that best describes the pain at its **average** in the last 7 days.
   ○0 ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10
   No Pain — Extreme Pain
4. Fill in the oval next to the one number that best describes the pain as it is **right now**.
   ○0 ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10
   No Pain — Extreme Pain

**Description of Function:**

Fill in the oval next to the **one number** that describes how during the past 7 days **pain has interfered** with your dog's:

5. **General Activity**
   ○0 ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10
   Does not Interfere — Completely Interferes
6. **Enjoyment of Life**
   ○0 ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10
   Does not Interfere — Completely Interferes

**Today's Date:** ☐☐ / ☐☐ / ☐☐ (Month / Day / Year) **Patient/Study ID#** _____

**Description of Function (continued):**

Fill in the oval next to the one number that describes how during the past 7 days **pain has interfered** with your dog's:

7. **Ability to Rise to Standing From Lying Down**
   ○0 ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10
   Does not Interfere — Completely Interferes
8. **Ability to Walk**
   ○0 ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10
   Does not Interfere — Completely Interferes
9. **Ability to Run**
   ○0 ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10
   Does not Interfere — Completely Interferes
10. **Ability to Climb Up (for example Stairs or Curbs)**
    ○0 ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10
    Does not Interfere — Completely Interferes

**Overall Impression:**

11. Fill in the oval next to the one response best describes your dog's overall quality of life over **the last 7 days**?
    ○ Poor ○ Fair ○ Good ○ Very Good ○ Excellent

**Fig. 1.** The Canine Brief Pain Inventory (If preferred, this can be omitted and a link to download the instrument www.caninebpi.com can be added to the body of the manuscript.

**Table I.** Similarities between human and canine naturally occurring osteoarthritis in companion dogs.

| | OSTEOARTHRITIS | | | |
|---|---|---|---|---|
| | | | Humans | Dogs |
| Pathology | Cartilage: | Proteoglycan loss, chondrocyte death, erosion | √ | √ |
| | Subchondral bone: | Increased turnover, thickening, neovascularisation | √ | √ |
| | Joint Margin: | Osteophytes | √ | √ |
| | Synovium: | Inflammation, fibrosis | √ | √ |
| | Joint capsule: | Fibrosis, enthesopathy | √ | √ |
| Sources of Joint Pain | Direct (nociceptors): Subchondral bone, ± joint capsule, ± osteophytes | | √ | √ |
| | Indirect (inflammatory cytokines, chemokines, neuropeptides): cartilage, ligaments | | √ | √ |
| Risk Factors | Obesity, age*, trauma* | | √ | √ |
| Diagnostic Modalities | Radiography, computerised tomography, magnetic resonance imaging, arthroscopy, synovial fluid analysis | | √ | √ |
| Therapeutic Goals | Control pain and improve function | | √ | √ |
| | Slow progression | | √ | √ |
| Outcome Assessment in Clinical Trials | Pain, mobility, stiffness, and function indices | | √ | √ |
| | Computerised gait analysis | | √ | √ |
| | Radiography & advanced imaging for disease modification | | √ | √ |

*Preclinical studies can be aligned with clinical disease by using older dogs with established disease or by undertaking studies to investigate interventions that prevent the onset or progression of disease following joint injury.

will ultimately be determined over time, as canine studies are used to inform the development of human analgesics.

While there are many reasons to believe that there is great potential for studies in dogs with osteoarthritis to shift the classical analgesic drug development paradigm towards one in which the results of animal studies more accurately predict the outcome of human clinical trials (Table I), the discussion must also be balanced with the impact of these studies on the companion animals that are enrolled, as well as animal health and welfare in general. Well designed, knowledgeably executed, and appropriately overseen companion animal studies can be a great benefit to animal health in general, as well as a great benefit to owners and their enrolled pets, regardless of whether or not their animal receives any direct benefit from an investigational intervention:

- Because there is generally not a third-party payer system in veterinary medicine, studies that are fully subsidised including diagnostics and other standard of care aspects of disease management, offer an opportunity for some pets to have access to care that they otherwise would not.
- Owners who enrol their dogs in studies are often very committed to the notion that, while their dog may not benefit directly from an intervention, their dog's participation in a study may benefit future pets and people.
- In the case of a successful intervention ultimately making it to the market, the off-label use of pharmaceuticals in veterinary medicine allows access to the new treatment option, even if it is never specifically developed and labelled for dogs.
- Because funding for clinical veterinary medical research is very limited, these subsidised studies enable increased understanding of the disease in companion animals, as well as the identifications of biomarkers, and the development of canine specific assays that may otherwise not be possible.
- In cases where companion animal studies can replace some studies in laboratory animals, this paradigm supports the principle of the 3Rs (Replacement, Reduction, Refinement) for humane use of animals in scientific research, by reducing the number of animals used in laboratory experiments

There is evidence that the results in companion dogs could reliably predict efficacy in humans. Across many classes of compounds in which there have been studies in companion animal chronic pain conditions and the same conditions in humans, the analogous results have been seen (68-75). In addition, many of the drugs used to treat pain in people have been successfully used off-label to treat pain in dogs as well. Only time will tell if preliminary indications of predictability will hold true as studies in companion dogs are embraced as potential missing link in the translation of osteoarthritis treatment from mice to men.

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