Where Does it Hurt? Pain management for musculoskeletal and neurologic conditions

Jessica Bunch, DVM, CCRT, CVA
Resident- Sports Medicine and Rehabilitation
Washington State University

Overview of pain

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. Nociception is the neural processes for encoding pain that leads to the perception of pain. This includes transduction, conduction, and central nervous system processing of nerve signals generated by the stimulation of nociceptors. Pain can be further divided into acute (adaptive) and chronic (maladaptive) pain.

Acute (adaptive) pain is considered protective, it has an easily identifiable cause, and is reversible. It can be composed of nociceptive and inflammatory pain. With nociceptive pain, a noxious stimulus activates high-threshold nociceptive primary afferent sensory neurons with cell bodies in the dorsal root ganglion and termination in the dorsal horn. The afferent signal is transmitted to the second order neuron and crosses over to the other side of the spinal cord, then is transmitted to the brain via ascending tracts in the spinal cord, where it is interpreted as a warning of actual or potential tissue damage. There is tonically active descending inhibition from the CNS that helps control whether the information from the primary afferent neuron is blocked at the level of entry into the dorsal horn of the spinal cord. Inflammatory pain is due to local tissue damage results in release of inflammatory mediators, recruitment of inflammatory cells and further release of inflammatory mediators. Mediators either sensitize sensory nerves, or directly stimulate them, resulting in a lowering of thresholds in sensory nerves and generation of action potentials (nociceptive signals). These signals are carried along the same pathway as described for nociceptive pain and descending inhibitory signals may dampen down the input at the level of the spinal cord. The increased sensitivity in the periphery associated with inflammatory pain following tissue damage promotes protection of the area, allowing it to heal.

Chronic (maladaptive) pain is defined as any long-standing pain of greater than 3-6 months in humans (probably around 3 months in animals). Chronic long-standing pain can be a complex mix of adaptive inflammatory and maladaptive pain and is not considered protective. The pathway is as described in 'adaptive' pain, but at the level of the dorsal root ganglion and the dorsal horn of the spinal cord there are changes (nervous system plasticity) resulting in amplification of the signals and facilitation of the signals. Additionally, descending inhibition is less effective which again facilitates the signals being transmitted from the periphery to higher centers. Hypersensitivity (increased pain from a stimulus that normally provokes pain) and allodynia (pain due to a stimulus that does not normally provoke pain) occur as a result of these changes, and in addition, spontaneous pain can occur due to abnormal activity in the nervous system.

Chronic pain is divided into neuropathic pain and functional pain. Neuropathic pain is due to direct damage to neural tissues such as damage to the spinal cord, peripheral nerves, or surgery. However, it is increasingly recognized that osteoarthritis and cancer may involve a degree of peripheral neuropathy via direct damage to the nerve endings or increased innervation that accompanies joint remodeling and angiogenesis. With functional pain, there is no damage or inflammation of the neural tissues and yet increased sensitivity to stimuli & spontaneous pain. Classic examples include

fibromyalgia and phantom limb pain. There is also increasing evidence of a functional pain component with osteoarthritis as well consisting of changes in the CNS which heightens sensitivity to pain and thus response (20-40% of people with OA have maladaptive pain component). Central sensitization (central plasticity) is initiated through cellular wind-up. Wind-up is a neuron's increasing response/output resulting from repeated, identical stimuli. This can result in a global response that lasts autonomously after the original stimulus has been discontinued or is sustained with low level nociceptor input from the periphery.

Assessing Pain

Pain can be divided into three domains: sensory-discriminative, cognitive-evaluative, and affective-motivational. The sensory-discriminative domain refers to the sensory perception of pain including location, severity, and duration. This can be assessed from history and physical exam including palpation. The affective-motivational domain refers to the emotional component of pain, also called the 'pain burden', and is assessed via history, pain scales, and quality of life scales. The cognitive-evaluative domain refers to the pain experience in relation to knowledge and past experiences. This can be difficult to assess in animals.

Pain assessment and pain scoring should be included as part of your vitals (along with your TPR). There are multiple pain scoring systems that can be taught to and utilized by you and your technicians. For acute pain consider the Colorado acute pain scale (dogs and cats), Glasgow composite pain scale (dogs or cats) or feline grimace scale. For chronic pain a few option include; the canine brief pain inventory (CPBI), feline musculoskeletal pain index (FMPI), client specific outcome measures (cats and dogs), and the Liverpool Osteoarthritis in Dogs (LOAD). There are more scoring systems than listed here, the main goal is pick one that is easy to train your staff, implement, and consistently use.

With chronic pain conditions many of these assessments can also be used to monitor response to therapy. Remember that with chronic pain, symptoms can be more subtle and maybe missed by owners, especially with cats. Some of the most common include decreased activity levels, decreased ability to perform activities (including jumping or decreased fluidity of horizontal movements), change in appetite (increased or decreased), inappropriate elimination, unkempt hair and nails, areas of alopecia, skin rippling, decreased socialization, general loss of interest (not playing, not wanting to go outside, etc), and/or sudden vocalization or agitation. For dogs, remember to assess them during transitions (sit to stand), at rest, walking and trotting. Videos can also be helpful to assess home behavior and for more subtle signs that may not be present in a clinical setting.

Pharmaceutical Considerations

There are a wide variety of pharmaceuticals that may be considered for pain control. Some of these are better suited for acute pain, others for chronic, and some for both. The key for pain control in both the acute and chronic setting is a multi-modal approach to pain management. This may include multiple pharmaceuticals in addition to non-pharmaceutical approaches and modalities.

The 2022 AAHA pain management guidelines for dogs and cats, was released in April and the authors developed a decision tree for pain management therapies based on a review of evidence-based medicine, practical considerations and experiences of the advisory board. As further clinical research is pursued, recommendations for each Tier will adapt and change. Please see the decision tree below:

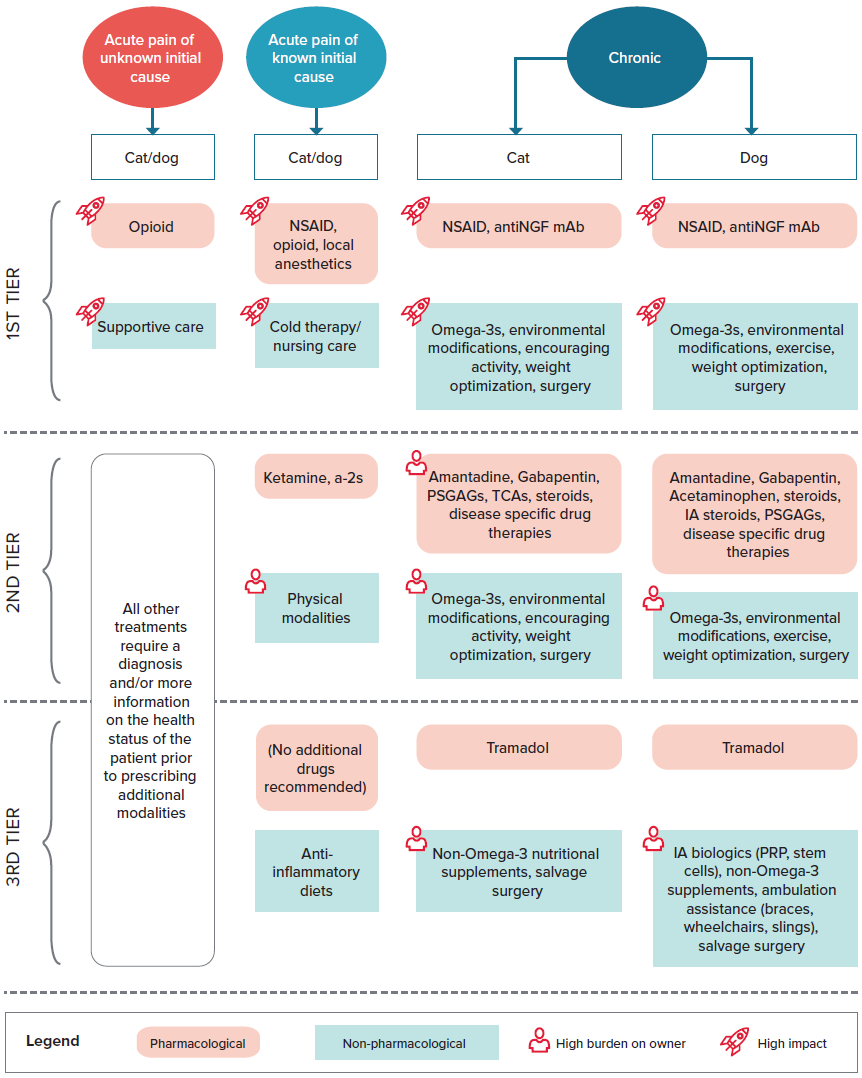

FIGURE 3

Decision Tree for Prioritizing Pain Management Therapies. This figure outlines a tiered approach to pain management in cats and dogs for acute and chronic pain. Tiers are presented from highest recommendation (most evidence for effectiveness) to lowest, although all therapies presented have some evidence to support their use. Physical modalities include laser therapy, pulsed electromagnetic field therapy, acupuncture, and transcutaneous electrical nerve stimulation. Surgical procedures for chronic pain include top-tier treatments such as dental procedures, removal of painful lesions, joint stabilization and replacement, and amputation; lower-tier (salvage) procedures including arthrodesis, denervation, and excision arthroplasty. Anti-NGF mAB, anti–nerve growth factor monoclonal antibody.

2022 AAHA Pain Management Guidelines

And now for a review on a few drugs…

NSAIDs

Non-steroidal anti-inflammatories (NSAIDs) are one of the most commonly prescribed and used medications for pain. In many cases they can be highly effective and appropriate but they may not be best suited for some conditions and certain patients with co-morbidities or sensitivities. Studies have shown that long term use of NSAIDs in dogs does not increase organ toxicity but rather increased efficacy with longer use.

NSAIDs inhibit the peripheral COX-2 enzyme to block the formation of prostaglandins such as PGE2 and PGI2, which function to dilate arterioles and sensitize peripheral nociceptors to the actions of mediators which produce localized pain and hypersensitivity. PGE2 produced by COX-2 plays a pivotal role in sustaining acute pain sensation by increasing nociceptor cyclic AMP, which decreases the nociceptor threshold of activation. Centrally, COX-2-mediated prostaglandins such as PGE2 are involved in spinal nociception and central sensitization. COX-2–activated PGE2 lowers the threshold for neuronal depolarization, increasing the number of action potentials and repetitive spiking.

Although there are currently no approved NSAIDs for chronic use in cats in the United States, both meloxicam and robenacoxib are approved in European countries for chronic use. Several studies have indicated that these can be used chronically in IRIS stage 1 and 2 cats, but monitoring is highly recommended. The low-dose chronic meloxicam dose has ranged from 0.02mg/kg to 0.05mg/kg daily to every 48 hours and robenacoxib at 1mg/kg daily.

Gabapentin

Although the exact mechanism of action is not known, gabapentin is believed to work through selectively inhibiting voltage-gated calcium channels containing the α2δ-1 subunit thereby reducing the release of pro-stimulatory neurotransmitters. This decreases nociceptive input through suppression of dorsal horn nociceptive neurons. Gabapentin is increasingly used for osteoarthritis and cancer pain as well as its role in neuropathic pain (both acute and chronic). More studies exist demonstrating its potential benefits in cats than dogs for chronic pain although lethargy and drowsiness were listed as common side effects. The common dosage range is 5-20mg/kg (although higher doses are listed) every 8 to 12 hours however many clinicians start at 10mg/kg. It has been demonstrated in cats, that reduced renal function may increase the side effects of gabapentin and therefore, dosages may need to be reduced in animals with chronic kidney disease.

NMDA Receptor Antagonists

NMDA receptor stimulation is associated with central neuronal sensitization and the wind-up pain. Amantadine and ketamine are both non-specific NMDA receptor antagonists that reduce central sensitization and activate descending inhibitory nerve activity. Ketamine has traditionally been considered a dissociative anesthetic but additionally is effective for both acute and chronic pain producing conditions.

Amantadine has been demonstrated in a study in dogs, to be effective at decreasing chronic pain when used with an NSAID. Typically, the dose is 3-5mg/kg once daily, however some data supports better effects at using it every 12 hours.

Although ketamine's activity as a NMDA receptor antagonist is the most widely understood, there is also evidence that it acts on a variety of additional receptors and sites. It has also been shown to reduce the occurrence of opioid induced hyperalgesia and also reduce undesirable opioid side effects like nausea. Ketamine also seems to impact the function and integration of various regions of the brain and may potentially directly impact neuroplasticity. Additionally, there is increased recognition of the relation between depression and chronic pain and in human medicine, ketamine is now being utilized for its anti-depressive effects. Low doses (0.2-0.5 mg/kg IV or SQ) of ketamine can also be used for chronic pain. There are no efficacy studies to support this use but anecdotal evidence and clinician

experience indicate that it is well tolerated with few side effects and beneficial when added to a multi-modal pain therapy plan.

Monoclonal Ab therapy

Monoclonal Ab therapy has been approved for use in cats and dogs in Europe for the last year and recently in the United States for cats with osteoarthritis. These products are called frunevetmab (Solensia®) for cats and bedinvetmab (Librela®) in dogs. More information to come in future presentations.

Acupuncture

A consensus statement by the National Institutes of Health found that acupuncture is deemed as safe or safer than many of our medications used to treat pain (in humans). In the human literature there is growing evidence to support its use for a multitude of conditions but most of the supportive research has been related to pain relief especially for musculoskeletal and neurologic conditions. In veterinary medicine, we have fewer studies but they have supported the use in post-operative pain and management of intervertebral disc disease. Given that acupuncture is well tolerated by most animals and is considered very safe, it is reasonable to consider it as an adjunctive modality for pain management.

Acupuncture involves inserting sterile, small filiform needles into specific locations (acupoints) to exert multiple physiological effects. These acupoints have been found to be locations that often have a higher density of mast cells, collagen fibers, small arterioles, lymphatics and nerves. Acupuncture's effects on reducing pain can be divided into local, segmental, and suprasegmental effects. Additionally, acupuncture can be useful in treating trigger points (hyper-irritable nodules in a muscle that produce local pain on palpation but can also cause referred pain and dysfunction), nausea, anxiety, depression, and more.

Local effects of acupuncture include the following: 1) Promotion of local healing and pain relief by stimulating sensory receptors (mechanoreceptors, nociceptors, thermoreceptors, etc.) 2) Release of inhibitory mediators (acetylcholine, norepinephrine, GABA, beta endorphins, somatostatin, nitric oxide, ATP , cGMP) and some stimulatory mediators as well. The main effect is on inhibitory mediators and there can also be a release of serotonin and histamine which can be inhibitory or stimulatory depending on the location. 3) Local blood vessels dilate to increase blood flow to the area.

Segmental effects involve the action potential from the needle insertion traveling to the spinal cord where they depress activity to the dorsal horn, thereby reducing its response to painful stimuli. The primary mechanism for this is the Gate Theory which is a concept that non-painful input closes the gates to painful input, which results in prevention of the pain sensation from traveling to the CNS (i.e., non-noxious input [stimulation] suppresses pain). Other segmental effects include decreased glutamate in the dorsal horn neurons, increased serotonin levels, inhibition of spinal glial cell activation, block of substance P release, and activation of spinal cord delta opioid receptors. Additionally it may modulate motor reflexes at the spinal cord level.

From the spinal cord, the action potentials travel up to the brain where we see our suprasegmental effects. These include: 1) Descending inhibition to the spinal cord to stop stimulating pain production neurons. 2) Activation of the serotonergic nucleus raphe magnus neurons (one of the

origins of the descending inhibitory pathways). 3) Activation of the noradrenergic neurons in the locus coereleus of the pons (which is involved in the physiologic response to stress and produces norepinephrine). 4) Stimulation of the hypothalmus to release beta-endorphins. 5) Activation of descending neurons of the periaqueductal gray matter which is the primary control center for descending pain modulation.

Weight management

Obesity is the most prevalent form of malnutrition in Western society. A 2018 study indicated that 59.5% of cats and 55.8% of dogs were classified as overweight or obese. Weight management is one of the keys in reducing discomfort and improving mobility especially in the arthritic patient. The Purina Lifespan study indicates that health risks in animals increases significantly at a body condition score of 6.7 out of 9. In a 2002 study by Kealy, et al. the mean age at which 50% of dogs required long term osteoarthritis treatment was 10.3years for moderately overweight dogs versus 13 years for ideal body conditions score dogs. Additionally, in a trial of lean fed versus control fed dogs, 10% of the lean fed dogs developed osteoarthritis by 8 years of life compared to 68-77% developed arthritis in the control fed group.

For more tools regarding weight management and nutrition, please visit https://wsava.org/global-guidelines/global-nutrition-guidelines/ and https://www.petnutritionalliance.org/.

Other

There are many other adjunctive therapies options for pain management such as physical rehabilitation (including exercise, cryotherapy, TENS), photobiomodulation (laser therapy), pulsed electromagnetic field therapy, and shockwave that will be discussed in more detail in future presentations.

Lastly there are a multitude of nutraceuticals/supplements that have been proposed to help with joint health and subsequently pain. Omega 3 fatty acids (DHA, EPA) have been shown to have anti-inflammatory effects and decrease symptoms of arthritis especially when fed in a therapeutic diet. Omega 3 fatty acids can also be supplemented, and the doses I use are 300-900 mg combined EPA+DHA per 10lbs daily (divided between meals). It is prudent to start at the low end of the dose and gradually work up to reduce the chances of soft stool/diarrhea. Perna canaliculus (green-lipped muscle) are a rich source of glycoaminoglycans, omega 3 fatty acids, and eicosatetraenoic acid (ETA) have been found to inhibit the activities of COX-2 and lipoxygenase. There have been a few studies that found improvement in arthritic scores, joint pain, and lameness in osteoarthritis dogs. PSGAGs (polysulfated aminoglycans) such as Adequan®, have also been shown to improve assessed lameness, range of motion, pain, orthopedic scores, and functional disability compared to placebo-treated control dogs. Other supplements to consider, with some evidence for efficacy, include egg-shell membrane complex and astaxanthin. Lastly, although there lacks consistent evidence for the use glucosamine/chondroitin supplements, anecdotally there seems to be some benefit that varies between individuals. Given that it is generally considered safe and well tolerated, these supplements may also be considered.

References

Gruen ME, Lascelles BDX, Colleran E, et al. 2022 AAHA Pain Management Guidelines for Dogs and Cats. *J Am Anim Hosp Assoc* 2022; 58:55–76. DOI 10.5326/JAAHA-MS-7292

Adrian D, Papich M, Baynes R, et al. Chronic maladaptive pain in cats: A review of current and future drug treatment options. *The Veterinary Journal* 230 (2017) 52–61

Monteiro BP and Steagall PV. CHRONIC PAIN IN CATS Recent advances in clinical assessment. *Journal of Feline Medicine and Surgery* (2019) 21, 601–614

Gaynor, James and William Muir. 2014. *Handbook of Veterinary Pain Management 3rd edition*. Mosby

Filshie, Jacqueline, Adrian White, Mike Cummings. 2016. *Medical Acupuncture: A Western Scientific Approach 2nd Edition* Elsevier