Stop the Suffering: Treatment Options for Chronic Pain

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Pain causes a myriad of adverse health effects mediated by the sympathoadrenal and neuroendocrine systems. Pain causes welfare concerns and impaired quality of life, like anorexia and insomnia, and behavior changes like fear/anxiety/stress and even aggression. Behavior changes can negatively impact the human-animal bond, which is a travesty for both the human and the pet and may cause loss of the client from the veterinary clinic. In addition, neuroplasticity (peripheral and central sensitization) leading to a continual worsening of pain is likely with un- or under-treated pain. Acute pain is largely protective and a normal survival process that 'protects' from injury or ongoing tissue damage. Acute pain is also called 'physiologic' or 'adaptive'. However, the neuroplastic changes from un- or undertreated acute pain can result in chronic pain. Because of pathophysiologic changes in the central nervous system, chronic pain can continue long after tissue healing. Since there is no longer healing tissue to 'protect', chronic pain serves '**no biological purpose**' and is called '**pathologic**' or '**maladaptive**' pain. Chronic pain can be difficult to treat and poorly responsive to conventional analgesic therapy. Chronic pain should be considered a terminal disease as inability to control pain is a major contributor to euthanasia.

Causes of chronic pain: As is the case in human medicine, osteoarthritis (OA) or degenerative joint disease (DJD) is the main cause of chronic pain in dogs and cats. Cancer is the second leading cause. As mentioned, un- or undertreated acute pain can also lead to chronic pain. Based on the population of aged dogs, it is estimated that 2 in 5 (40%) adult dogs are likely to have some form of OA. Based on radiographic evidence, 22% of the general cat population (Godfrey 2005) and 90% of cats over 12 years old (Hardie EM, et al. 2002) may have OA. In dogs, large-breed, high-level of activity, age > 7 years and obesity are all risk-factors for development of OA. Weight loss is an important part of therapy! Current evidence in cats only links geriatric age as a risk factor, but obesity may play a role in degree of pain. If diagnosed after the disease has become moderate to severe, the disease is more complex and multimodal therapy will likely be required and even aggressive therapy may not completely eliminate all pain. Thus, it is imperative that we promote identification of OA early in the disease process by **emphasizing the signs of OA pain to our clients and to our staff members** who may be involved in patient physical examinations and/or pain-related discussions with pet owners.

Analgesic drugs: According to the new AAHA Pain Management Guidelines for dogs and cats (Gruen et al. J Am Anim Hosp Assoc 2022 Mar 1;58(2):55-76; https://www.aaha.org/aaha-guidelines/2022-aaha-pain-management-guidelines-for-dogs-and-cats/home/), the most predictable and profoundly effective drugs for treatment of chronic pain in dogs and cats are non-steroidal anti-inflammatory drugs (NSAIDs) and anti-nerve growth factor monoclonal antibodies (antiNGF-mAbs).

AntiNGF-mAbs: Nerve growth factor (NGF) is a potent pain generator and propagator, perhaps even more potent than prostaglandin. Nerve growth factor (NGF) binds to tropomyosin receptor kinase A (Trk-A) receptors on peripheral nerve endings, resulting in nociceptor depolarization and the potential for peripheral sensitization. NGF also binds to Trk-A receptors on pro-inflammatory cells like mast cells, resulting in the release of more inflammatory mediators which contribute to the development of peripheral sensitization. In addition, the NGF-TrkA complex is transported to the cell body in the dorsal root ganglia (DRG), where it modulates or increases expression of other receptors and ion channels involved in pain production (eg, transient receptor potential vanilloid 1, acid-sensing ion channels, bradykinin receptors, voltage-gated sodium channels, voltage gated calcium channels and mechano-

transducers; Enomoto et al. 2018). This causes phenotypic alterations in primary afferent fibers, which leads to increased excitability and a further contribution to peripheral sensitization. In addition, NGF/TrkA-mediated transcriptional changes occur, resulting in increased expression of pronociceptive neurotransmitters (eg, substance P, calcitonin gene-related peptide (CGRP) and brain-derived neurotrophic factor). With the increased nociceptive input to the dorsal horn neurons in the spinal cord, central sensitization is highly likely to develop. With the development of peripheral and central sensitization, pain becomes intense – perhaps even intolerable – to the patient.

Monoclonal antibody drugs are a leading platform for drug development because they have several advantages over most traditional pharmaceuticals including, injection rather than oral route of administration; long duration of action (4+ weeks;, targeted inactivation of specific proteins or cytokines with minimal (depending on the protein) adverse effects; and elimination of the drug through protein catabolism and recycling rather than hepatic and/or renal clearance. One mAb drug, Cytopoint®, is already available in veterinary medicine. The new anti-nerve growth factor monoclonal antibodies, which are species-specific for dogs (bedinvetmab, Librela®) and cats (frunevetmab, Solensia®), have proven highly efficacious with minimal adverse effects for the treatment of osteoarthritis pain. Frunevetmab is now the first FDA-approved chronic pain drug for cats in the US. For a thorough review of the anti-NGF mAb and more information on its use for OA in veterinary medicine see Enomoto et al. 2018 (OPEN ACCESS, available at https://www.zoetisus.com/oa-pain/canine-oa-pain.aspx. As stated, nerve growth factor is a potent pain generator and propagator, perhaps even more potent than prostaglandins.

NSAIDs: Non-steroidal anti-inflammatory drugs (NSAIDs) are effective since most forms of chronic pain have an inflammatory component. NSAIDs provide analgesia AND treat pain at its source (inflammation). Multiple NSAIDs are approved for treatment of chronic pain in dogs. In some countries, there are no approved NSAIDs for treatment of chronic pain in cats, but there are guidelines and clinical reports demonstrating safety & efficacy of NSAIDs when administered at the correct dose to cats. **Both meloxicam and robenacoxib are approved in some countries for treatment of both acute and chronic pain in cats.** The meloxicam dose most commonly used for chronic pain in cats is 0.03-0.05 mg/kg PO SID, often with a loading dose of 0.1 mg/kg. Dosages as low as 0.01 mg/kg/SID may be effective (Gunew, et al. 2008) and perhaps even beneficial – or at least not harmful - in some cats with chronic kidney disease (Gowan, et al. 2012; Gowan, et al. 2011). Robenacoxib is approved at 1-2.4 mg/kg (which is also the dose range for acute pain) for a duration 'decided on an individual basis' (robenacoxib European product label). The author commonly uses 1 mg/kg SID, or less frequently if effective, for treatment of chronic pain in cats.

Grapiprant is a 'piprant', or prostaglandin receptor antagonist anti-inflammatory drug. Grapiprant specifically antagonizes the EP4 receptor of PGE2. This receptor mediates pain and inflammation associated with OA. Because other prostaglandins are not blocked, those involved in homeostasis are not affected and the adverse effects commonly associated with traditional NSAIDs (eg, gastrointestinal upset & ulceration and renal & kidney damage) are decreased (Rausch-Derra LC et al 2015)). At the time this manuscript was written, grapiprant was not approved in cats but published safety study indicated a wide safety margin in cats (Rausch-Derra & Rhodes, 2016).

Gabapentin: Gabapentin can be effective in treating neuropathic pain. Neuropathic pain is pain from nervous system pathology and includes conditions that cause direct pathology of the nervous system (eg, herniated discs, nerve root tumors), pressure on nerves (eg, osteophytes near nerves) or nerve damage (eg, trauma, surgery – especially when large nerves are cut). **In addition, the pathologic changes that occur in the pain pathway in response to chronic pain stimulation cause neuropathic pain**. There are few published research studies on the analgesic effects of gabapentin in dogs and cats

but the drug is commonly used for control of various pain syndromes. In one of the few published studies, a dose of 10 mg/kg gabapentin BID improved owner-identified impaired activities in osteoarthritic cats (Guedes et al 2018). In dogs with neuropathic pain secondary to Chiari malformation, the addition of gabapentin was more effective in improving quality of life than carprofen alone (Plessas et al 2015). The dosage generally ranges from 3-10 mg/kg PO BID to QID but dosages as high as 50 mg/kg BID have been anecdotally reported. Generally, gabapentin therapy should be initiated at 10 mg/kg PO BID and dosages/dosing frequency increased as necessary. Starting as dosages as low as 3-5 mg/kg BID may be necessary (see chart below). The most common side effect is sedation and the dose of gabapentin should be reduced in patients that become sedate. Gradually increasing the dose over time generally eliminates the chance of sedation. However, sedation is not necessarily an adverse effect if it allows the patient to get restful sleep. So increasing night-time dosages but not day-time dosages can be beneficial both for the pet's sleep (and subsequently sleep for the owners!) and for decreasing pet-owners concerns regarding sedation. Gabapentin-mediated ataxia can occur, especially in older, larger dogs with decreased muscle mass. This can make the dog seem 'worse' to the owners and, unfortunately, does not resolve with time. Thus, gabapentin should be discontinued if ataxia occurs.

This is a recommended gabapentin treatment guideline – **the dosing escalation for patients in moderate-severe pain is fairly 'aggressive' in this guideline**, but this approach is often necessary for analgesic efficacy in patients with this level of pain:

- Start at 5 mg/kg for mild pain and 10 mg/kg BID for moderate to severe pain.
    - If the patient has renal or hepatic disease, the starting dose may be as low as 3 mg/kg BID (see more under adverse effects).
- If no pain relief occurs in 3-5 days (can extend to 7-10 days if pain is mild), use the same dose TID.
- If no pain relief occurs in another 3-5 days (can extend to 7-10 days if pain is mild) or if TID dosing is not possible, increase the dose by roughly 25% per dose.
- Continue escalating every 3-5 days (can extend to 7-10 days if pain is mild) until one of the two endpoints is reached (sedation or pain relief).
- If sedation is reached before pain relief, return to the previous (non-sedating) dose and maintain at that dose for 7 days.
- If the patient is comfortable, stay at that dose. If not comfortable, try increasing again. Gradually increasing the dose over time often decreases the incidence of sedation.
- If sedation without pain relief occurs a second time, we presume that gabapentin will not be effective and change therapeutic plans. Often the plan still includes gabapentin but with more multimodal therapy.
- The If the patient is to be removed from gabapentin therapy (eg, the patient is 'cured' or the gabapentin is not working), the drug should be gradually withdrawn over a period of one to three weeks (depending on the duration of therapy) to prevent potential rebound pain.
    - Have the owner continue to monitor the patient. Drug efficacy is sometimes easier to identify when the drug is being withdrawn.

Gabapentin can be compounded as a liquid, which may be easier to administer to cats. Gabapentin in a lipid formulation may be absorbed when applied to the ears of cats (Slovak JE, Costa AP. JVIM 2021;35(4):1981-1987). Although, as with many drugs, pinna absorption is not predictable.

Pregabalin: The mechanism of action of pregabalin is the same as that for gabapentin but the drug undergoes linear pharmacokinetics, making dosing easier. Pregabalin is widely used in human medicine for treatment of a variety of chronic pain conditions. Research in animals is limited but has, for example,

been shown to alleviate central pain from syringomyelia in Cavalier King Charles Spaniels (Thoefner et al. 2019; Sanchiz-Mora et al. 2019).

Other Anxiolytics/Antidepressants: Antidepressants are a common addition to pain management in humans. Their role in the pain pathway is in the descending inhibitory limb, which is a feed-back mechanism from central centers to the spinal cord. The tricyclic antidepressant amitriptyline at 3–4 mg/kg PO BID may be an effective component of a multimodal protocol in some patients (Moore 2016). In human medicine, serotonin and norepinephrine reuptake inhibitors (SNRIs; duloxetine, venlafaxine, desvenlafaxine, and milnacipran) are used for pain relief but no data are available for vet patients.

Tramadol: Tramadol may have some efficacy via the SNRI mechanism. Cats also have an opioid effect but dogs produce little of the intermediate (M-1) opioid metabolite that is likely responsible for a good deal of tramadol-mediated analgesia. Tramadol used alone in dogs is unlikely to provide analgesia for OA pain (Budsberg et al 2018). Tramadol was effective at controlling osteoarthritis pain in cats (Monteiro et al 2017) but the margin between the effective dose and the dysphoric dose is very narrow. Cats really dislike the taste of tramadol.

Ketamine: Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist and plays a role in both anesthesia & analgesia. Activation of the NMDA receptors in the dorsal horn of the spinal cord are, in large part, responsible for the pain of central sensitization (or 'wind up). By antagonizing these receptors, the pain pathway can be returned to 'normal'. Meaning that the patient may still feel pain (thus ketamine must be part of a multimodal protocol) but that the pain is not exaggerated and is more likely to be controlled by traditional analgesic drugs like NSAIDs and opioids. To achieve this effect, ketamine must be administered as an infusion. The analgesic effects in chronic pain have been well-documented in humans (Remerand et al. 2009; Sigtermans et al. 2009; Cohen et al. 2018), although, as with any treatment of any chronic condition, a ketamine infusion does not always produce analgesia (Sen et al. 2009). This may be because the pain in those patients is not caused or augmented by central sensitization. In veterinary medicine, ketamine improved postoperative analgesia after forelimb amputation for up to 3 days (Wagner et al. 2002). There are no publications to guide ketamine infusions in dogs and cats for chronic pain but an infusion of 2-10 microg/kg/min following a loading bolus of 0.2-0.5 mg/kg is a common protocol. The duration of the infusion is not known. Ideally, the infusion would be administered until the patient demonstrates decreased pain but this is unlikely to be practical. Anecdotal reports include everything from 2 to 24 hours but the common range is 2-6 hours. The infusion is repeated 'as needed', which could be anything from never again to weekly. As stated, this is part of a multimodal protocol and the goal is to return quality of life to the patient but not necessarily to eliminate any other analgesic therapies.

Amantadine: Amantadine is an antiviral drug that also antagonizes the N-methyl-D-aspartate (NMDA) receptors, an action which prevents or reverses the development of central sensitization but does not provide direct analgesia. In humans, the NMDA-receptor antagonists are being extensively researched and have been used for treatment of acute, chronic and 'specialized' (eg, neuropathic and phantom limb) pain conditions. Newer NMDA-receptor antagonists (eg, memantine) are available in human medicine. The role of amantadine in pain management has been reported in dogs by Lascelles et al (2008). Effective pain control was achieved when amantadine was combined with an NSAID and dosed at 5 mg/kg orally for 21 days. A recent literature search yielded no other veterinary publications describing the use of amantadine for analgesia. Amantadine has a variety of uses in chronic pain and should be added to the treatment protocol anytime pain of 'wind-up' could be an issue. Scenarios include: NSAIDs suddenly 'not working' after controlling pain long-term, long standing untreated pain,

moderate to severe cancer pain. Amantadine should be dosed at 2-7 mg/kg SID-BID (**BID is recommended**) for at least 3 weeks. It can be made as a compounded liquid, which may be easier to administer to cats.

Opioids: Opioids are not traditionally used – and are not the most effective drug class – for treatment of chronic pain but may be necessary for profound pain and for break-through pain. Opioids to consider include transdermal fentanyl and oral formulations of codeine, codeine + acetaminophen (DOGS ONLY), morphine, oxycodone, hydrocodone and methadone. These opioids are DEA scheduled (fentanyl, codeine and morphine are Class II, codeine with acetaminophen is Class III) and have a high potential to cause adverse effects (primarily sedation, nausea and, eventually, constipation). Research trials have shown poor evidence that orally delivered opioids are effective for analgesia because of their low bioavailability (KuKanich 2013) but clinical use supports their efficacy in some patients. Fentanyl patches can be used in times of severe break-through pain or for 'end-stage' pain when a few days of pain relief prior to euthanasia are needed.
Buprenorphine (Class III) can be administered on the oral mucosa for both acute and chronic pain in cats but absorption is not as good as was once thought (Giordano, et al. 2010), so recommended dosages may be higher this route of delivery to 0.03-0.05 mg/kg BID-QID. Occasionally, very low dosages are surprisingly effective. Transdermal buprenorphine is FDA-approved for cats and could potentially be useful for break through pain
For all patients with chronic opioid use, consider that constipation may occur and increase dietary fiber.

Lidocaine infusions: In human medicine, perioperative lidocaine infusions have been shown to prevent the development of chronic pain (Bailey et al. 2018). Lidocaine infusions have also been shown to play a role in treatment of chronic pain and reduction of opioid need (Kandil et al. 2017). The dose is the low-end of the dose used for treatment of acute pain or arrhythmias. Remember that lidocaine infusions may be dangerous for cats.

Maropitant?: Although there are no studies on the use of maropitant to treat chronic pain, maropitant likely provides analgesia through antagonism of neurokinin-1 (NK-1) receptors in the pain pathway. Since maropitant can be administered orally, it is an option for owners to use at home and is anecdotally dosed at 2 mg/kg PO SID for conditions like chronic pancreatitis. Administer as long as needed.

Intra-articular:
Steroids: Perhaps systemically, but better – targeted pain therapy like steroid epidurals (methylprednisolone acetate [eg, DepoMedrol] 0.1 mg/kg) or joint injections (methylprednisolone acetate – 'dose' is generally by volume which is limited by joint size but should not exceed 0.1 mg/kg).
Intra-articular Medical Devices
A veterinary medical device is defined by the FDA as a product that provides function without pharmacological, chemical, or metabolic action.
Naturally derived collagen and elastin
Spryng™ is an intra-articular device that is 'indicated for use in both horses and small animals to aid in the management of lameness issues, joint pain and osteoarthritis from loss of cartilage or tissue-bone mechanical malfunction caused by joint dysfunction not associated with infection.' The product is a 'shock-absorbing matrix that works with synovial fluid to mimic the protective form and function of natural, healthy joint cartilage.' Provides up to 1-year of action. (Reference: https://www.sprynghealth.com/small-animal-how-it-works)
Radioactive Tin: Synovetin OA® is approved for intra-articular treatment of osteoarthritis elbow pain in dogs. The device uses 'novel, conversion electron therapy using Tin (117mSn)' The product 'emits low-

energy electrons that cause targeted elimination of inflamed synovial cells'. Anecdotally used in joints other than the elbow. Provides up to 1-year of pain relief. (Reference: https://www.synovetin.com/how-synovetin-oar-works)

Nonpharmacologic Therapy

Techniques reported useful for treatment of OA-mediated pain include everything from simple heat/cold therapy to more advanced techniques like physical therapy/rehabilitation, acupuncture and massage. In addition to the modalities just listed, modalities like therapeutic ultrasound, transcutaneous electrical nerve stimulation (TENS), pulsed radio frequency and low-level laser may all contribute to pain relief but, as with nutraceuticals, most of the evidence of efficacy is weak at best. However, physical therapy/rehabilitation and acupuncture have more positive evidence than the other modalities and many pain practitioners incorporate these techniques into their OA treatment plans. An advantage of the simpler nonpharmacologic therapies is that owners can often be trained to utilize basic techniques at home and the pet can then benefit from more consistent therapy. Owners can be taught to utilize ice packs, heat compresses, basic exercise and physical therapy maneuvers, basic massage, and acupressure. As stated with nutraceuticals, lack of evidence of efficacy does not mean that these treatment modalities are ineffective in all patients and the modalities should be considered as a viable part of multimodal analgesia, especially in patients where other therapies have failed, or as stand-alone treatment when pharmacologic therapy is inappropriate for the patient or when the nonpharmacologic therapy is effective when used alone. Here is a list of proposed modalities with references to utilize if you are interested:

Acupuncture: Strong evidence of efficacy (Petty MC, Huntingford JL. Evidence-Based Application of Acupuncture for Pain Management in Companion Animal Medicine Vet Sci 2022 May 26;9(6):252; Silva et al. Effect of acupuncture on pain and quality of life in canine neurological and musculoskeletal diseases. Can Vet J. 2017 Sep;58(9):941-951; Fry et al. Acupuncture for analgesia in veterinary medicine. Topics in Companion Animal Medicine 29;2014:35–42).

Physical therapy/rehabilitation: Strong evidence of efficacy of various physical therapy/rehabilitation modalities for treatment of chronic pain (Lamoreaux Hesbach A. Manual therapy in veterinary rehabilitation. Topics in Companion Animal Medicine 29;2014:20-23).

Massage: Corti L. Massage therapy for dogs and cats. Topics in Companion Animal Med 29;2014:54-57.

Laser: Gross DM. Introduction to therapeutic lasers in a rehabilitation setting. Topics in Companion Animal Medicine 29;2014:49-53.

Myofascial trigger point release: Wall R. Introduction to myofascial trigger points in dogs. Topics in Companion Animal Medicine 29;2014:43-48.

Stem cells: There is moderate evidence in both humans and animals (examples: Kim et al. 2019; Sasaki et al. 2019; Shah et al. 2018) that stem cell administration can decrease pain from osteoarthritis. The limitations are cost (several thousand dollars per treatment) and need for anesthesia/sedation. There are several types of stem cells (eg, umbilical cord, mesenchymal) supplied from a variety of sources (autologous [patient's own cells], allogeneic [cells from a donor of the same species], xenographic [cells from another species, generally human umbilicus]).

Pulsed electromagnetic field therapy (PEMF): Gaynor JS, et al. Veterinary applications of pulsed electromagnetic field therapy. Res Vet Sci. 2018;119:1-8.

Shock wave: Increasing evidence. Example publication: Alvarez L. Extracorporeal Shockwave Therapy for Musculoskeletal Pathologies. Vet Clin North Am Small Anim Pract 2022;52(4):1033-1042.

Platelet rich plasma (PRP): Increasingly strong evidence. Example publication: Alves JC, Santos A, Jorge P. Platelet-rich plasma therapy in dogs with bilateral hip osteoarthritis. BMC Vet Res. 2021;17(1):207.

'Chondroprotective' compounds
Injectable polysulfated glycosaminoglycan (PSGAG) is FDA-approved for the treatment of OA in dogs (Adequan®) in the US and pentosan polysulfate (Cartrophen) is used in Canada. The evidence for efficacy is moderate, with some patients not responding and some having a profound response. It is commonly used in cats at the same dose used in dogs. An advantage of this compound is that it can be administered SQ by the owner at home, which means that some patients may be more likely to get treated since the cat doesn't have to come to the hospital. However, because any improvement that does occur is fairly slow, these compounds should be used as adjunctive therapy to NSAIDs or other rapidly-acting, more potent analgesic drugs when pain is moderate to severe.

Dietary supplements, nutraceuticals
Evidence supporting the efficacy of many compounds is fairly sparse and not always scientifically based. However, evidence for efficacy of undenatured collagen type II, omega 3 fatty acids and green lipped mussel compounds warrants use.

Other compounds:
Cannabinoids (CBD): Efficacy is controversial in human medicine, where more studies on the products are available. In veterinary medicine, numerous studies are underway but only one has been published to date ((Gamble et al. 2018). A good review on the topic from human medicine is: VanDolah HJ, Bauer BA, Mauck KF. Clinicians' Guide to Cannabidiol and Hemp Oils. Mayo Clin Proc. 2019 Sep;94(9):1840-1851 (OPEN ACCESS). Because cannabinoid receptors are present in the pain pathway, the compounds are likely to have efficacy – albeit potentially mild since the main site of action appears to be the descending inhibitory limb of the pain pathway. However, currently studies are limited by legal issues and product ingredients and purity are not regulated.

Pain Identification/Assessment: The biggest hurdle to treating chronic pain is getting patients with chronic pain into the hospital. Increased utilization of tools to identify – and to help pet owners identify – pain in animals should be a major drive in every practice. It is almost impossible that more patients with chronic pain are presented to the veterinary clinic for treatment than are left at home to suffer from unidentified – and thus untreated – chronic pain. Unfortunately, animals rarely exhibit pain in the veterinary clinic unless palpation and targeted questions for the client are used. Chronic pain is best assessed by the owner at home and is usually assessed by 'quality of life' (QOL) changes rather than pain scores. It is difficult for owners (and often veterinarians) to detect pain in their pets but easier to detect the impact of that pain on the pet's QOL. Since the main concern regarding untreated/ undertreated pain is affective changes and decreased QOL, this is not only the easiest but also the most appropriate way to assess pain. Various pain assessment forms are available for the owner to use at home. In addition, it is helpful if owners video the pain behavior at home and share the video during the pet's appointment at the clinic. Websites with useful information for veterinarians – and for pet owners – on identification of chronic pain includes:
https://www.zoetisus.com/oa-pain/feline-screening-resources.aspx and https://www.zoetisus.com/oa-pain/canine-oa-pain.aspx
https://www.orthoassist.elanco.com/us/en/coast
https://painfreecats.org/
Conclusion: Chronic pain can drastically alter a patient's quality of life and can, unfortunately, be difficult to treat. In order to obtain adequate pain control, multimodal therapy should be utilized in every patient with moderate to severe pain. Also, unfortunately, the number of drugs and techniques that are available to treat chronic pain is fairly limited and knowledge of the use of these drugs and

techniques in dogs and cats is even more limited. However, because chronic pain is a major problem in human medicine as well as veterinary medicine, research into the relief of chronic pain is extensive. Hopefully, new drugs and techniques developed for humans will rapidly become available to our veterinary patients.

Dosages for drugs other than NSAIDs used to treat chronic pain in dogs and cats. Not all drugs / dosages are approved for use. PO=oral, SC=subcutaneous, IM=intramuscular, IV=intravenous, OTM=oral transmucosal. SID=once daily, BID=twice daily, TID=three times daily, QID=four times daily. Listed in alphabetical order – not necessarily by order of preference.

Drug	**DOG Dosage mg/kg unless otherwise stated**	**CAT Dosage mg/kg unless otherwise stated**	**Comments**
Amantadine (Various capsules, liquid)	2-7 PO SID-**BID** for at least 21 days	2-7 mg/kg PO SID-**BID** for at least 21 days	Does not provide analgesia directly but helps prevent / treat wind-up due to NMDA receptor antagonist activity. Use in multimodal protocol.
Amitriptyline	3-4 PO BID	3-4 mg/kg PO BID	Serotonin-reuptake inhibition may provide analgesia through the descending inhibitory limb of the pain pathway. Some proof of this in humans. Tastes bad and $$.
Anti-NGFmAb	Minimum 0.5-1.0 mg/kg	Minimum 1 mg/kg LABEL: 1 **mL** cats 2.5-7.0 kg; 2 **mL** 7.1-14 kg	As of 2022, cat approved in US, dog in other countries. SQ administration provides 4+ weeks of analgesia.
CBD oil	2 PO BID	Unknown	Gamble LJ, et al. Front Vet Sci. 2018 Jul 23;5:165.
Gabapentin (multiple tablet or capsule sizes; liquid)	3-20 PO BID-QID; up to 50; usually start with 5-10	3-20 PO BID-QID; up to 50; usually start with 5-10	Effective for treatment of neuropathic pain. Best used as part of a multimodal protocol. Increase the dose by about 25% every 5-14 days (depending on pain severity) until patient is more comfortable or sedate. If sedate, go back to previous dose.
Ketamine (100 mg/ml) infusion	5-15 microg/kg/ min for minimum of several hours. Optimal duration unknown.	5-15 microg/kg/ min for minimum of several hours. Optimal duration unknown.	Can be used to 'break' the cycle of severe pain. Does not provide analgesia directly but helps prevent / treat wind-up due to NMDA receptor antagonist. Use in multimodal protocol.
Ketamine (100 mg/ml) SC	0.5 mg/kg	0.5 mg/kg	At least weekly to start. Up to every day or every other day for severe pain, monthly may provide maintenance analgesia
Lidocaine infusion	25-50 microg/kg/min	CONTROVERSIAL 10-25micg/kg/min	Combine with ketamine. Optimal infusion duration unknown.
Maropitant	1-2 PO SID	1-2 PO SID	Perhaps best for visceral pain?

Pentosan polysulfate (eg, Cartrophen [CA])	Use label dose	Use dog dose	Not scheduled for cats. Clinically most effective for mild pain or as part of a multimodal protocol.
Polysulfated Glycosamino-glycan (eg, Adequan)	4 IM twice a week for up to 4 weeks, max 8 injections (label dose)	4 IM or SQ twice a week for up to 4 weeks, max 8 injections (dog dose)	Licensed by the FDA for control of OA pain in dogs (not licensed in cats). Clinically most effective for mild pain or as part of a multimodal protocol. Uptake following SQ injection proven in cats.
Pregabalin	4 PO BID	1-2 PO BID	No analgesic studies. Can cause sedation.
Tramadol (50 mg tablets)	2-5 PO BID -QID. Low bioavailability, needs frequent dosing. Up to 10 mg/kg?	2-5 mg/kg PO BID-TID. Start with 2 mg/kg BID. High bioavailability, likely to cause dysphoria.	Tramadol is an 'opioid like' drug that has other mechanisms of action. The pharmacokinetics in the dog are somewhat erratic so the drug is best used as multimodal therapy with NSAIDs or other analgesic drugs. **DEA CONTROLLED.**
Opioids			Chronic use may cause constipation. **DEA CONTROLLED. Maybe used for break-through pain.**
Oral morphine (10,15,30 mg tablets)	0.5-2 PO TID - QID (can be dosed as often as q2-4hrs)	0.25-0.5 mg/kg PO TID-QID (can dose as up to q 3-4 hrs)	Higher doses may induce sedation or dysphoria. Nausea & vomiting may also occur but tolerance to these effects generally develops within 1 week.
Sustained release oral morphine	2-5 PO BID - QID	Difficult to dose due to size of tablets (don't cut tablets)	Higher doses may induce sedation or dysphoria. Increase the frequency of administration prior to increasing dose if duration is not long enough
Codeine (15, 30, 60 mg tablets)	1-2 PO q6-8 hrs	0.1-1.0 mg/kg PO 4-8 hrs	Higher doses may induce sedation or dysphoria. Nausea & vomiting may also occur but a tolerance to these effects generally develops within 1 week.
Codeine30-60 mg + acetaminophen (300 mg)	1-2 (codeine) PO q 8-12 hr	**TOXIC TO CATS - DO NOT USE**	Multimodal therapy improves analgesia over either drug used alone. DO NOT EXCEED 10-15 mg/kg acetaminophen per dose.
Transdermal fentanyl	3-5 ug/kg/hr	3-5 ug/kg/hr	May induce sedation or dysphoria. Adding NSAID may improve analgesia.
Methadone (various)	0.6 q 4-8 hrs OTM	0.6 mg/kg q4-8 hrs OTM	Absorbed transmucosally in cats – not yet proven in dogs but used anecdotally.
Buprenorphine (0.3mg/ml)	0.01-0.03 SC, IM, IV; 0.03-0.05 OTM	0.01-0.03 SC, IM, IV; 0.03-0.05 OTM	May cause mild opioid side effects.

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