New Ways to Help: Osteoarthritis Treatment Update

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Acute versus Chronic pain

Acute and chronic pain differ in ways other than their duration. *Acute pain* typically follows some tissue insult such as surgery or trauma and the pain resolves as the injury heals. Acute pain is called 'protective pain' because its role is to protect the patient from further tissue damage by limiting use of injured tissues. Acute pain tends to be responsive to treatment with conventional drug therapy including NSAIDs, alpha-2 agonists, and opioids. *Chronic pain* can exist after the original injury has healed as a result of pathophysiologic changes in the central nervous system. Since there is no longer an injury to 'protect', chronic pain serves to no purpose and is called 'pathologic' or 'maladaptive' pain. Chronic pain can be difficult to treat and poorly responsive to conventional analgesic therapy. Effective treatment may require multiple pharmacologic and non-pharmacologic treatment modalities (i.e., various analgesic drugs, acupuncture, massage, physical therapy, weight control, etc...). Left untreated, chronic pain causes a deterioration of the animal's quality of life and may result in adverse behavioral changes, including aggression.

As is the case in human medicine, osteoarthritis (OA) is the main cause of chronic pain in dogs and cats. Based on the population of aged dogs in many countries, it is estimated that 1 in 5 adult dogs is likely to have some form of OA. OA is most often seen in large-breed dogs, patients older than 7 years of age, patients having a history of being very active and overweight patients (thus, weight loss is an important part of therapy). Based on radiographic evidence, 22% of our general cat population (Godfrey DR. J Small Anim Pract. 2005;46(9):425-9) and 90% of cats over 12 years old (Hardie EM, et al. J Am Vet Med Assoc. 2002;220(5):628-32) may have OA. Fortunately, chronic pain due to OA - if diagnosed early - is often responsive to weight loss, controlled exercise, non-steroidal antiinflammatory drugs (NSAID) or piprants, and/or disease modifying agents (eg, chondroitin sulfate). If diagnosed after the disease has become moderate to severe, multimodal therapy will probably be required and even aggressive therapy may not completely eliminate all pain. Thus, it is imperative that we emphasize the signs of OA to our clients and to our staff members who may be involved in patient physical examinations.

Cancer is the second most common cause of chronic pain in animals. Although geriatric pets are most frequently affected, cancer can occur at any age. Patients will almost always require a multi-modal approach to pain therapy and may also require a variety of non-pharmacologic analgesic therapies (eg, acupuncture) as well as a number of analgesic adjunctive medications (e.g. NMDA antagonists). Neuropathic pain, a type of pain caused by a true lesion in the nervous system, is increasingly recognized in veterinary patients. Unfortunately, neuropathic pain can be extremely severe and is also quite difficult to control. Often there is no relief of neuropathic pain from traditional analgesic drugs like NSAIDs and opioids.

Treatment of chronic pain

As stated, treatment of chronic pain is not always easy and often requires a combination of therapies ('multimodal analgesia'). This combination may include multiple pharmaceuticals, pharmaceuticals plus non-pharmacologic therapy (eg, acupuncture, massage, etc..) or both. Often, finding an effective treatment takes time and must proceed on a 'trial and error' basis. It is important to remember – and important to explain to the client - that chronic pain is a very individual disease and treatment protocols almost always require modification for each individual patient. Treatment of chronic pain is most effective when the clinic staff operates as a pain management team. However, a pain management strategy for treating chronic pain will not work unless the pet's owner is also a part of the team. The owner should be educated as to the underlying condition that causes pain, as well as to the effects and side effects of the analgesic therapy. Furthermore, the owner must be committed to long-term therapy and to assessing the extent of their pet's pain and relief of pain from analgesics. Various pain assessment forms are available for the owner to use at home and one is included in Table 1. Also, owners should be advised that adequate pain control involves more than just treatment of the pain itself. Weight loss is extremely

important in overweight patients and alteration of the pet's environment (eg, eliminate need for pet to climb stairs, cover slick floors with mats or rugs to provide better footing, etc…) and activity level (eg, more controlled activity like leash walking is often the best for a pet in pain) are often part of the treatment plan.

TABLE 1: Analgesic assessment for the owners of pets in chronic pain to fill in at home. (modified from 'Pain Management for the Small Animal Practitioner'. Tranquilli et al; published by Teton New Media, Jackson, WY)

	DATE			
PAIN INTENSITY How bad was your pet's pain today?	Severe Moderate Mild None	Severe Moderate Mild None	Severe Moderate Mild None	Severe Moderate Mild None
PAIN RELIEF How much pain relief was achieved by the medication?	Complete Good Moderate Slight None	Complete Good Moderate Slight None	Complete Good Moderate Slight None	Complete Good Moderate Slight None
SIDE EFFECTS Did the medication upset your pet in any way? Please describe.				

Analgesic drugs

A good review of the pharmacokinetics of oral analgesics used for the treatment of chronic pain in dogs and cats has been published (KuKanich 2013).

Multimodal therapy

Effective treatment of moderate to severe chronic pain almost always requires multimodal therapy. What options are available when the patient is unable to take NSAIDS or, more commonly, when the pain advances to a pain state that is uncontrollable by NSAIDs used alone? In that instance, opioids, N-methyl-D-aspartate (NMDA) antagonists, and novel drugs like gabapentin should all be considered as potential therapies. In addition, non-pharmacologic therapies (eg, acupuncture, massage, physical therapy, TENS, etc…) should be strongly considered. Dosages for drugs used to treat chronic pain, along with considerations for the use of the drugs, are listed in Table 2.

NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are the mainstay of treatment of chronic pain. This is an appropriate choice since most forms of chronic pain do have an inflammatory component. NSAIDs provide analgesia AND treat pain at its source (inflammation). Controlling the pathology of the pain leads to more effective pain relief. NSAIDs are the only drugs that have statistically shown consistent relief of chronic pain. Multiple NSAIDs are approved for treatment of chronic pain in dogs. There are no FDA approved NSAIDs for treatment of chronic pain in cats, but there are guidelines and clinical reports demonstrating safety and efficacy of NSAIDs when administered at the correct dose to cats.

The meloxicam dose most commonly used for chronic pain in cats is 0.03-0.05 mg/kg/SID. This can be administered daily or less frequently, if possible. Dosages as low as 0.01 mg/kg/SID may be effective (Gunew MN, et al. J Feline Med Surg. 2008;10(3):235-41) and perhaps even beneficial – or at least not harmful - in some cats with chronic kidney disease (Gowan RA, et al. J Feline Med Surg. 2012;14(12):876-81; Gowan RA, et al. J Feline Med Surg. 2011;13(10):752-61). There are no studies on the use of robenacoxib for chronic pain but there is a published study reporting safety when the drug was used for 42 days (King JN, et al. J Vet Pharmacol Ther. 2012;35(3):290-300.). Anecdotally, the label dose is commonly used SID or less frequently for treatment of chronic pain in cats.

Piprants
Piprants are prostaglandin receptor antagonists and grapiprant is currently the only drug in this class. Grapiprant 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 minimal to nonexistent. At the time this manuscript was written, grapiprant was not yet FDA-approved in cats but a safety study has been published (Rausch-Derra LC, Rhodes L. Am J Vet Res. 2016;77(7):688-92.).

Gabapentin
Gabapentin is commonly used to control seizures in both human and veterinary patients. In addition to the antiseizure activity, gabapentin has been shown to 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. Although no research manuscripts are available regarding the use of gabapentin in dogs and cats for the treatment of chronic pain, many practitioners are using the drug for control of various pain syndromes. The dosage generally ranges from 1-10 mg/kg PO BID to QID but dosages as high as 50 mg/kg have been anecdotally reported. Generally, gabapentin therapy is initiated at 3-10 mg/kg PO BID and dosages increased as necessary. 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. Recommended gabapentin treatment guideline:

- 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, use the same dose TID.
- If no pain relief occurs in another 3-5 days or if TID dosing is not possible, increase the dose by roughly 25% per dose.
- Continue escalating every 3-5 days 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.

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 rebound hyperalgesia. Gabapentin has a variety of uses in chronic pain and scenarios for addition of gabapentin should include:

- Patients with painful backs/necks
- Any patient with known nerve damage
- Patients with difficult to diagnose, difficult to characterize pain
- Patients with long standing chronic pain

Opioids

Tramadol is probably the most commonly used opioid for treatment of chronic pain in veterinary patients. Tramadol is a centrally acting analgesic drug that is structurally related to both codeine and morphine and does have some opioid effects. However, tramadol also inhibits both serotonin and norepinephrine uptake. These varied activities are complementary and synergistic for analgesia and have led to the classification of tramadol as a 'nontraditional centrally acting analgesic'. However, tramadol provides analgesia that is moderate at best and the drug should be used as part of a multimodal protocol rather than as a stand-alone drug. This is further evidenced by the fact that absorption of tramadol is highly variable in dogs and it is not possible to predict which dogs might absorb the drug poorly, resulting in inadequate analgesia for that patient. In dogs, the systemic availability following 11 mg/kg of orally administered tramadol was 65 ± 38% and the half-life (t½) was 1.71 ± 0.12 hrs (Kukanich & Papich, 2004), which is much shorter than the t½ in human beings. Furthermore, dogs produce very little of the intermediate (M-1) metabolite that is likely responsible for a good deal of tramadol-mediated analgesia. When compared to dogs, bioavailability was greater (93±7%) and the t½ was longer (204±8 mins) in cats following 5 mg/kg tramadol administered orally (Pypendop & Ilkew, 2008; Papich & Bledsoe, 2007). Furthermore, cats produced a significant concentration of the active M-1 metabolite, which also had a long t½. Thus, there are more opioid mediated effects, including analgesia and dysphoria, from administration of oral tramadol in cats when compared to dogs.

The tramadol dose for the dog and cat is 2-5 mg/kg BID to QID. Because of the high bioavailability and production of the active metabolite in cats, a starting dose of 2 mg/kg BID is recommended. Dogs, conversely, generally require TID-QID dosing for effective pain control and dosages of up to 10 mg/kg are used anecdotally. Tramadol can cause opioid-mediated side effects in dogs, including sedation and mild cases of anorexia, nausea and constipation. Tramadol could potentially cause serotonin reuptake syndrome when combined with other selective serotonin reuptake inhibitors (SSRIs; fluoxetine (Reconcile® or Prozac®), paroxetine (Paxil®), sertraline (Zoloft®) and fluvoxamine (Luvox®)) or serotonin-norepinephrine reuptake inhibitors (SNRIs; Cymbalta (duloxetine), Effexor (venlafaxine)), although the use of tramadol at appropriate dosages has not been reported to cause serotonin reuptake syndrome (reports are all due to a significant tramadol over dosage). Serotonin receptor-antagonists and reuptake inhibitors (SARIs; trazodone) might also interact with tramadol.

Other opioids used in veterinary medicine include transdermal fentanyl and oral formulations of codeine, codeine + acetaminophen (DOGS ONLY), morphine, oxycodone, hydrocodone and methadone. These opioids are more potent than tramadol and should be considered anytime that pain is severe or when pain has advanced beyond the point that it can be controlled by tramadol. These opioids are DEA scheduled (fentanyl, codeine and morphine are Class II, codeine+acetaminophen is Class III) and have a greater potential to cause adverse effects (primarily sedation, nausea and, eventually, constipation) than tramadol but are more likely to control severe pain. 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. Buprenorphine (Class III) can be administered bucally for both acute and chronic pain in cats but new information has shown that absorption is not as good as was once thought (Giordano, et al. 2010), so recommended dosages have been increased for this route of delivery to 0.03-0.05 mg/kg BID-QID.

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 scenarios for addition of amantadine include:

- Anytime pain of 'wind-up' could be an issue
- NSAIDs suddenly 'not working' after controlling pain long-term
- Any long standing untreated pain
- Moderate to severe cancer pain

Amantadine should be dosed at 5-7 mg/kg SID-BID (BID is recommended) for at least 3 weeks.

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), 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 2-6 microg/kg/min is fairly common. 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' – generally every 30 days. 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.

Other drugs
Because chronic pain is so difficult to treat, new drugs – or new applications for old drugs – are continually being investigated. Currently, other drugs to consider for treatment of chronic pain include antidepressant drugs (eg, the tricyclic antidepressants, SNRIs, SSRIs, etc.), bisphosphonates and newer generations of currently used drugs like pregabalin (newer generation of gabapentin) and tapentadol (newer generation of tramadol).

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.

Special diets, dietary supplements, nutraceuticals & other disease-modifying compounds
Most of the diets and food supplements are designed to modify the disease progression of OA and are thus called 'disease modifying osteoarthritis agents' (DMOAA). The idea of disease modification is a step in the right

direction for disease elimination, but evidence supporting the OA-modifying efficacy of most diets, dietary supplements and nutraceuticals is fairly sparse and not always scientifically based. A good review of a number of these products is available (Fox 2009) and the author of that review states, 'Perhaps the best advice for pet owners is to spend their money where the science is strong' (Fox 2009).

However, it does appear that some of compounds may modify the progression of OA, especially diets rich in eicosapentaenoic acid (EPA) (Fox 2009) and at least one of the polysulfated glycosaminoglycan (PSGAG) chondroprotective compounds (Fox 2009). In fact, there is one injectable) PSGAG available that is FDA-approved for the treatment of OA in dogs (Adequan®). 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. As a caveat to this discussion, because chronic pain has many facets and inciting causes, some of the DMOAAs with little evidence may still work in a particular patient. Lack of evidence does not necessarily mean lack of efficacy for an individual patient, but does decrease the likelihood that the efficacy would be apparent in a global population of patients.

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.

Some common scenarios with treatment recommendations *(see table for dosing info):*

1. A patient with mild OA has been on an NSAID for a week and the NSAID isn't working to control pain.
   - Solution: Try another NSAID. Individual sensitivity exists in animals just like it exists in human beings. ALL NSAIDs work globally, but each individual may respond better to one NSAID than to another.
2. A patient (dog or cat) with mild OA has been on an NSAID for an extended duration of time and the NSAID was controlling pain adequately until recently. Now, despite the fact that the disease doesn't seem to be worsening, the patient is fairly painful.
   - Solution: Add amantadine to the current therapy. The most common explanation for this scenario is that the chronic stimulation of the NMDA receptors in the dorsal horn of the spinal cord has produced central sensitization. The NSAID should remain to treat the inflammatory component of OA.
3. A patient (dog or cat) with moderate OA or cancer pain is painful even on an NSAID.
   - Solution: Add gabapentin to the NSAID and send home tramadol (or another opioid), either on a continuous basis or an 'as needed' basis. The opioids in cancer patients are generally administered on a continuous basis. If this is a cat, consider using OTM buprenorphine as the opioid.
4. A patient with disc herniation is very painful but is not a candidate for surgery.
   - Solution: Add gabapentin to the NSAID (or steroid) treatment and use tramadol (or another opioid) either as continuous therapy or on an 'as needed' basis. For severe pain, hospitalize the patient for several hours of a ketamine infusion.
5. A cat has pain of OA and elevated renal enzymes but the owner would like to try to improve the cat's quality of life.
   - Try a joint health modifier like Adequan or Cosequin. These are often very successful in cats. NSAIDs may also be appropriate as evidenced by cats with confirmed renal failure receiving meloxicam for chronic OA pain with no detrimental renal effects (Gowan et al 2012).

TABLE 2: 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.

Drug	Dog Dosage	Cat Dosage	Comments
Opioids			Chronic use of opioids may cause constipation.
Tramadol (50 mg tablets)	2-5 mg/kg (up to 10 mg/kg?) PO BID - QID. Frequent dosing recommended due to low bioavailability.	2-5 mg/kg PO BID-TID. Start with 2 mg/kg BID because of high bioavail-ability in the cat.	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.
Oral morphine (10,15,30 mg tablets)	0.5-2 mg/kg PO TID - QID (can be dosed as often as q2-4hrs)	0.25-0.5 mg/kg PO TID-QID (can be dosed as often as q3-4 hrs)	Higher doses may induce sedation or dysphoria. Nausea & vomiting may also occur but a tolerance to these effects generally develops within 1 week.
Sustained release oral morphine (15, 30, 60, 100, 200 mg tablets)	2-5 mg/kg PO BID - QID	Difficult to dose due to size of tablets (tablets should not be cut)	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 mg/kg 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.
Codeine (30 or 60 mg) plus acetaminophen (300 mg)	1-2 mg/kg (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 (25, 50, 75, 100 µg/hr)	3-5 ug/kg/hr	3-5 ug/kg/hr	May induce sedation or dysphoria. Addition of an NSAID may improve analgesia.
Methadone (5, 10 mg tablets)	0.1-0.5 mg/kg IM, SC q 2-4 hrs	0.1-0.5 mg/kg IM, SC q 2-4 hrs	Side effects same as other opioids. Only injectable dosing currently published.
Buprenorphine (0.3mg/ml inject.)	0.01-0.03mg/kg SC, IM, IV; 0.03-0.05 OTM	0.01-0.03 mg/kg SC, IM, IV; 0.03-0.05 OTM	May cause mild opioid side effects. Volume too large to be practical in anything larger than a cat or small dog.
Other drugs or compounds			
Amantadine (Various capsules, liquid)	2-5 mg/kg PO SID-**BID** for at least 21 days	2-5 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.
Ketamine (100 mg/ml)	2-4 microg/kg/ min for several hours. Optimal duration of infusion is unknown.	2-4 microg/kg/min for several hours. Optimal duration of infusion is 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 activity. Use in multimodal protocol.
Gabapentin (multiple tablet	1-10 mg/kg PO BID-QID; up to 40	1-10 mg/kg PO BID-QID; up to 40	Effective for treatment of neuropathic pain. Best used as part of a multimodal protocol.

or capsule sizes; liquid has xylitol)	mg/kg (start with 3-10 mg/kg)	mg/kg (start with 3-10 mg/kg)	Increase the dose by about 25% every 3-7 days until patient is more comfortable or sedate. If sedate, go back to previous dose.
Polysulfated Glycosamino-glycan (eg, Adequan)	Inject 2mg per lb given only by intramuscular (IM) injection twice a week for up to 4 weeks (a maximum of 8 injections)	Inject 2mg per lb given only by intramuscular (IM) injection twice a week for up to 4 weeks (a maximum of 8 injections)	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.