**Introduction:**
Apart from the NSAID and opioid classes of NSAID analgesics can be found a broad array of other pain-modifying medications and strategies.

**Alpha 2 agonist**
Medetomidine and dexmedetomidine binds opioid-like receptors on C- and A-delta fibers, especially in the central nervous system. Binding pre-synthaptically, NE production is reduced and sedation occurs; binding post-synaptically, analgesia is produced, and is profoundly synergistic with opioids. It also blocks NE receptors on blood vessels, resulting in vasoconstriction; the resulting hypertension parasympathetically induces bradycardia, which is extended by a subsequent direct decrease in sympathetic tone. However, central perfusion is maintained (including in cats\(^1\)) and wide use can be made for these alpha-2 agonists in acute and peri-operative setting, especially at lower-than label doses in combination with opioids +/- ketamine. One particularly novel and user-friendly utility is IV micro-doses intra- and post-operatively, 0.25 – 1.0 mcg/kg (although dosing of cats and small dogs presents a challenge since doses may be as low as 0.001 ml of the current dexmedetomidine product in the U.S.). One small study of cats with HCM revealed medetomidine to actually increase the ventricular outflow.\(^2\) A popular use of alpha 2 agonists is to combine with ketamine and an opioid, and administered intramuscularly. This so called “Kitty Magic,” for which many formulations abound, provides for dose-dependent sedation, analgesia, immobilization, and in some cases, a surgical plane. One study revealed that out of 10 cats sedated with dexmedetomidine 25 mg/kg, ketamine 3 mg/kg, and buprenorphine 30 mcg/kg IM, 7 were able to proceed with orchiectomy without the need for supplemental gas anesthesia (1, and none, required no supplemental analgesia with butorphanol 0.2 mg/kg, and hydromorphone 0.05 mg/kg, respectively).\(^3\)

The utility of OTM dexmedetomidine, combined with buprenorphine, has been evaluated in in healthy adult cats. Although pharmacokinetics are inferior to IM administration\(^4\), and the OTM route elicited salivation, there were comparable levels of sedation and antinociception to IM dosing.\(^5\)

**Sub-anesthetic ketamine CRI**
A phencyclidine dissociative anesthetic, the evidence is building for its pre-emptive and preventive effects when given at subanesthetic doses in an intravenous constant rate infusion. Ketamine binds to a phencyclidine receptor inside the NMDA receptor, i.e. the calcium channel would already have to be open and active for ketamine to exert its effect. However, once bound, it decreases the channel’s opening time and frequency, thus reducing Ca+ ion influx and dampening secondary intracellular signaling cascades. Hence it is unlikely (and has not been shown) to be truly analgesic in nature. Rather, it appears to be protective against hyperalgesia and central hypersensitization in the post-operative setting,\(^6\) including in the dog.\(^7\) One study in the cat revealed ketamine CRI to raise both thermal and mechanical thresholds.\(^8\) To achieve sub-anesthetic CRI, 60 mg (0.6 ml of 100 mg/ml) ketamine can be added to 1 L of fluids. Administering the fluids at customary intra-operative rates of 5-10 ml/kg/hr will deliver 5-10 mcg/kg/min of ketamine; and slowing to a customary maintenance rate of 2 ml/kg/hr will deliver 2 mcg/kg/min of ketamine. A loading dose of 0.5-1.0 mg/kg IV is advised to rapidly achieve plasma levels that the CRI would then sustain. Utilizing most any of the dexmedetomidine/ketamine/opioid protocols, or inducing with ketamine/valium IV (or alternatively, likely Telazol\(^8\)) will provide the loading dose. Alternatively, a combination ketamine (2 mg/kg) / propofol (2 mg/kg) IV induction protocol was described in cats\(^9\) which also (more than) provides the loading dose for continuing ketamine CRI.

**Systemic Lidocaine CRI**
The mechanisms behind a pain-modifying effect of systemic lidocaine remain an area of investigation but appear to include its ability to enter the nociceptor cell body in the dorsal root ganglion. In humans the evidence is strong for safety and the beneficial effects of intravenous lidocaine (IVL) on pain after abdominal surgery in humans (although not other surgeries eliciting somatic pain)\(^10\) and possibly horses, including both pain and return of bowel function. Systemic, intravenous infusion of lidocaine has also been shown to elicit a sustained effect on neuropathic pain in humans,\(^11\) although this has not been studied in companion animals. It is anesthetic sparing in dogs and cats, but current evidence for a pain-modifying effect in these species remains inconclusive.\(^12\) One OHE-model study in dogs found IVL to be non-inferior to meloxicam for post-op pain\(^13\), and EEG changes in the dog appear to be consistent with an anti-nociceptive effect.\(^14\) IVL can still be suggested as a safe and sparing adjunct to opioid and other analgesics for abdominal surgery, trauma, and pancreatitis at a dose of 50 mcg/kg/min, in dogs; and this has been used for 24 – 48 hours. Systemic, intravenous infusion of lidocaine has also been shown to elicit a sustained effect on neuropathic pain in humans,\(^15\) and may have a specific point of action in the brain.\(^16\) Some investigators
discourage the use of IVL in cats due to negative cardiovascular effects, but anecdotally has been utilized in clinical practice.

**Tramadol**

Tramadol is a Schedule IV drug that in humans has opioid and serotonin- and norepinephrine (inhibitory neurotransmitters) agonism. In contradistinction to the dog, the cat displays favorable pharmacokinetics and pharmacodynamics. This species does make the M1 (opioid) metabolite and the oral form has been shown to increase thermal thresholds as well as demonstrate a pain-modifying effect in an ovariohysterectomy model and in osteoarthritis. Case series have been published utilizing oral tramadol peri-operatively. It is a bitter drug that cats may not readily accept, but compounded palatable formulations have been reported. It is important to note that we have no veterinary dose-titration, reliable safety or toxicity data in cats (or dogs), cats may be more sensitive to tramadol’s extrapyramidal effects and toxicities are reported.

Tramadol should be used only very cautiously with other serotoninergic or monoamine-enhancing medications such as tricyclic antidepressants, mirtazapine, and others. Customary doses for tramadol in the cat are in the 3 mg/kg range.

Tapentadol acts similarly to tramadol with the parent compound rather than metabolites having the opioid, serotoninergic and noradrenergic effects. Antinociceptive effects of tapentadol is demonstrable but dose-titration and toxicity studies still need to be performed prior to recommendation for clinical use.

**Gabapentin**

Gabapentin is labeled for use as an anti-convulsant drug but is in widespread human use for its analgesic properties, purported to be mostly through interaction with the alpha-2-delta subunit of the voltage gated calcium channel. There is good kinetic data on dogs and cats, suggesting a TID dosing schedule. Rodent studies demonstrating a pain-modifying effect in OA. There are case reports describing using long-term gabapentin for musculoskeletal and back pain, in the treatment of Feline Orofacial Pain Syndrome, Feline Hyperesthesia Syndrome, and one trial demonstrated an anti-hyperalgesic effect in feline OA. Anecdotal experience is favorable as an adjunct medication for DJD along with NSAID and remains one of its most popular utilities. The primary adverse effect of somnolescence can be mitigated by starting off at quite low doses and tapering upwards, e.g. beginning at 3-5 mg/kg and tapering upwards every 1-2 weeks to a target dose of 15-20 mg/kg BID (and sometimes higher). Gabapentin has been used in the acute, peri-surgical setting. Several other meta-analyses and systematic reviews in humans seem to support this conclusion, in addition to other outcome measures such as decreased opioid consumption and time to discharge. The dose utilized in these studies is generally in the 10 mg/kg range, given pre-op and several doses TID post-op. In cats, gabapentin was not MAC-sparing nor did it increase thermal thresholds. However, there is a case report of using it in cases of acute injury in 2 cats and anecdotal experience may be favorable. Additionally, gabapentin has been utilized at a high dose for its sedating, anxiolytic effect to facilitate travel to the veterinarian’s office; customary it is a100 mg (20 mg/kg for a 12-lb cat) whose contents are mixed with food (and a flavor enhancer such as Fortiflora or Zyklene). Similarly, gabapentin has demonstrated utility in humans to reduce preoperative anxiety and pain catastrophizing in highly anxious patients prior to major surgery.

**Amantadine**

Amantadine exerts a pain-modifying effect as an NMDA receptor antagonist and remains an interest in humans with chronic and neuropathic pain (but not specifically osteoarthritis) in humans, with mixed results. One study at 3 mg/kg once daily does demonstrate utility as an adjunct to NSAID in dogs with refractory osteoarthritis within 3 weeks, and there is one case report of using amantadine to treat neuropathic pain in a dog. The pharmacokinetics of amantadine in cats has been established, with a high oral bioavailability and favorable plasma T ½ (5-6 hours). More recent pharmacokinetic studies suggest that 3-5 mg/kg every 12 hours may be more appropriate. Clinical utility in cats is strictly anecdotal at this time. Toxicity and kinetic studies have been performed in humans, and in dogs, anecdotal reports of amantadine-induced ADE’s include agitation and other behavioral changes, and GI signs especially diarrhea. In humans QT-syndrome is reported, and in dogs a recent study demonstrated a moderate risk of arrhythmia and decreased cardiac output in halothane-anesthetized dogs receiving IV amantadine. The clinical significance of these findings in cats is unknown.

**Tricyclic Anti-depressants**

TCA’s exert their analgesic activity by enhancing synaptic norepinephrine and serotonin (inhibitory transmitters) in the dorsal horn of the spinal cord, although it has other effects including anti-histamine, anti-cholinergic, NMDA receptor antagonism, and sodium channel blockade. It has a balanced NE and serotonin effect, and thus is among the more sedating, anti-cholinergic, and effective of various TCA’s. As a class, TCA’s are the most effective medications for neuropathic pain in humans. However in cats the literature is restricted to idiopathic cystitis (also
now termed “Pandora Syndrome” for its description as a somatic pain syndrome). In humans TCA’s can have an unfavorable side effect profile which limit their use for neuropathic pain despite their efficacy (dry mouth, sedation, PU/PD, urine retention, blurred vision, hypotension, weight gain, agitation, seizures, cardiac arrhythmia, BM dyscrasia). Customary doses of amitriptyline are 1-2 mg/kg BID in the cat, but a recent review article suggests 3-4 mg/kg based on its PK profile in these species and anecdotally appears to be well-tolerated. The transdermal route in cats is poor.

Selective Norepinephrine Reuptake Inhibitors

These compounds exert their effect by increasing serotonin +/- norepinephrine in the synaptic cleft. At least one popular SSNRI, duloxetine, has a chronic pain label in humans (including osteoarthritis and low back pain, in addition to fibromyalgia and diabetic neuropathy). There are conflicting data about bioavailability and other pharmacokinetics in dogs and no data at all in cats. There are PK data of another SSNRI in dogs, venlafaxine (which has evidence for efficacy in human OA), bioavailability approaching 50% of that of humans and T ¾ of 3 hours with a suggested dose of 4 mg/kg PO Q 8-12H, but not in cats. Evidence of a clinical pain-modifying effect for either molecule is currently lacking in animals, and there are no dose-titration data for either drug. SNRI’s appear to be a safe class of drug in cats. In one case series of toxicities, only ¼ of cats w/ known ingestion became symptomatic with the most common AE sedation (75%) followed by GI signs (50%); CNS stimulation and CV signs 13%. There was 100% survival with general supportive care.

Maropitant

Maropitant (Cerenia®) inhibits binding of Substance P to the NK-1 receptor. Acting in the Vomiting Center of the brain, it serves as an anti-emetic, but in the spinal cord a pain-modifying effect is hypothesized. The true pain-modifying effect in dogs and cats remains uncertain, and no published data in cats are available. One study in dogs revealed an anesthetic-sparing effect but utilized a very high-dose IV infusion of maropitant, and another a non-modifying effect in dogs and cats remains uncertain, and no published data in cats are available. One study in dogs revealed an anesthetic-sparing effect but utilized a very high-dose IV infusion of maropitant, and another a non-modifying effect in dogs and cats remains uncertain, and no published data in cats are available.

Parenterally-administered poly-sulfated glycosaminoglycans (PSGAG) has regulatory approval as safe and effective chondroprotectants in dogs, and is supported by independent studies. Although not an analgesic drug per se, a clinical effect can be said to be conferred by minimizing the release of pro-inflammatory cytokines (e.g. IL1, PGE2) and degradative enzymes (e.g. metalloproteinases). Adequan™ (Luitpold) is labeled in dogs for 4.4 mg/kg IM twice weekly for 4 weeks. However, extra-label long-term use is commonly employed, generally administered chronically, subcutaneously, and in cats. Bioavailability and joint distribution in cats is supported by a study of radio-labeled SC administration.

Anti-NGF Mab

Originally identified for its role in embryonic development of the nervous system, Nerve Growth Factor (NGF) is now known to have the ability to alter the function of nociceptors in the adult. NGF is upregulated in inflamed tissues, binds to Trk-A receptors on nociceptor endings there, and contributes to pain and peripheral sensitization. Microglial cells in the dorsal horn of the spinal cord constitute a significant source of NGF which can be induced into excess production under circumstances of glial activation (see below), thus also contributing to central hypersensitization. NGF is responsible for several physiologic aberrations of pain processing: this includes but is not limited to sprouting of terminal nerve endings and thus promoting “cross-talk” between numbers and types of neurons that ordinarily would not have been involved in pain processing (creates the circumstance of expanded field of pain, and the experience of hyperalgesia and allodynia).

Several different NGF-antagonism strategies have been explored, and at least 4 companies working to develop specifically an anti-NGF monoclonal antibody product for humans suffering from OA, low back pain, and cancer pain. FDA Phase II, III trials for OA were conducted for the molecules tanezumab, fulranumab, REGN475. In 2010 efficacy in reducing pain was established but several individuals developed osteonecrosis and avascular necrosis. The trials were halted, but in 2012 the FDA authorized continuation of trials with narrowed patient inclusion criteria. Veterinary therapeutic anti-NGF Mab products (ranevetmab canine, frunevetmab feline, www.nexvet.com, since purchased by Zoetis) are in developmental stages, utilizing a patented the technology (PETisation™) that enables rapid translation of mouse or human proteins for the treatment of other species (caninization and felinization). Initial efficacy data appears encouraging for 1 month of pain-modifying effect in canine and feline OA.

Cannabinoids
The cannabinoid system is now well-established to facilitate pain modulation, although the exact mechanism remains an area of intense study. Several different CB receptors are described but of special interest for pain modification are the CB1 and CB2 sub-types on pre-synaptic neurons in the central nervous system, although a number of other receptors may also be in play. They are G-protein coupled (as are opioid PGE2 receptors) and generally speaking when activated decreases the release of neurotransmitters (glutamate, acetylcholine, dopamine) into the synaptic cleft, which hyperpolarizes the post-synaptic neuron. CB1 (predominantly located in the brain and spinal cord, but also visera and adipose tissue) also modulates opioid, NMDA, and GABA receptors on the post-synaptic side; CB2 receptors are found in highest concentrations on immunoregulatory cells, including microglia. CB1 and CB2 are generally down-regulated in a healthy state, but become up-regulated in both neurons and microglia with injury or inflammation. Pharmacologically, the goal is to selectively enhance this aspect of the cannabinoid system without activation of central adverse effects including psychotropic activity. Targets include developing selective synthetic CB agonists to achieve this effect, antagonizing degradative enzymes of endogenous cannabinoids anandamide (AEA) and 2-arachidonylglycerol (2-AG), and inhibiting the re-uptake of AEA and 2-AG. Several cannabinoid-ergic molecules are on the market or in development for the treatment of neuropathic pain.

Diet:
A study of OA cats receiving an EPA- and DHA-fortified diet revealed owners to perceive some aspects of behavior modification are the CB1 and CB2 sub-types on pre-synaptic neurons in the central nervous system, although a number of other receptors may also be in play. They are G-protein coupled (as are opioid PGE2 receptors) and generally speaking when activated decreases the release of neurotransmitters (glutamate, acetylcholine, dopamine) into the synaptic cleft, which hyperpolarizes the post-synaptic neuron. CB1 (predominantly located in the brain and spinal cord, but also visera and adipose tissue) also modulates opioid, NMDA, and GABA receptors on the post-synaptic side; CB2 receptors are found in highest concentrations on immunoregulatory cells, including microglia. CB1 and CB2 are generally down-regulated in a healthy state, but become up-regulated in both neurons and microglia with injury or inflammation. Pharmacologically, the goal is to selectively enhance this aspect of the cannabinoid system without activation of central adverse effects including psychotropic activity. Targets include developing selective synthetic CB agonists to achieve this effect, antagonizing degradative enzymes of endogenous cannabinoids anandamide (AEA) and 2-arachidonylglycerol (2-AG), and inhibiting the re-uptake of AEA and 2-AG. Several cannabinoid-ergic molecules are on the market or in development for the treatment of neuropathic pain.

These include Sativex® (nabiximols, GW Pharmaceuticals, UK; an oral mucosal spray for pain associated with multiple sclerosis, and under investigation for chemotherapy-evoked neuropathy) and Cesamet® (nabilone, Meda Pharmaceuticals, Somerset NJ; labeled as an anti-emetic but used as adjunct therapy and under investigation for fibromyalgia, diabetic neuropathy, and phantom limb pain). These products appear to have low toxicity; some patients report dry mouth and dizziness, but a safety review of medical cannabinoids found 96.6% of AE’s to be non-serious. A complete review of the recent human literature regarding cannabinoids in pain management is available, and a recent systematic review made variable recommendations regarding the use of cannabinoids in human neuropathic pain depending on the specific condition and type of cannabinoid utilized. A commercial cannabinoid product is available in the U.S. for dogs and cats (Canna-Pet®) but it is not FDA-approved nor are any data available regarding its content, efficacy, safety, or other quantitative analyses.

Non-pharmacologic modalities:

Low-Stress, Fear-Free Handling:
The AAFP/ISFM Feline-Friendly Handling Guidelines (Rodan I, Sundahl E 2011) is an excellent place to begin, and the manuscript is accompanied by video demonstrations: http://www.catvets.com/guidelines/practice-guidelines/handling-guidelines. Dr. Sophia Yin’s body of work is probably the most comprehensive dedicated to this subject are, in particular: Low Stress Handling, Restraint and Behavior Modification of Dogs and Cats: Techniques for Developing Patients Who Love Their Visits and website, www.drsophiayin.com. AAHA is partnering with the Fear Free program of training and certification: www.fearfreepets.com. Facial pheromones (e.g. Feliway®) are increasingly recognized for their integral role in diminishing stress, perhaps especially in cats and part of low-stress and fear-free handling.

Diet:
A study of OA cats receiving an EPA- and DHA-fortified diet revealed owners to perceive some aspects of behavior and locomotion to improve. Although these results are encouraging, the outcome measures were not validated for OA-related pain in cats.

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