The robust advances in pain management for companion animals underlie the decision of AAHA and AAFP to expand on the information provided in the 2007 AAHA/AAFP Pain Management Guidelines for Dogs and Cats. The 2015 Guidelines can be found at these URL’s:

https://www.aaha.org/public_documents/professional/guidelines/2015_aaha_aafp_pain_management_guidelines_for_dogs_and_cats.pdf and
http://jfm.sagepub.com/content/17/3/251.full.pdf+html

The Guidelines continue the trend in all branches of medicine toward evidence-based consensus statements that address key issues in clinical practice. Although not a review article, the Guidelines represent a force multiplier for the busy practitioner, consolidating in a single place current recommendations and insights from experts in pain management. The recommendations of the guidelines Task Force are evidence based insofar as possible and otherwise represent a consensus of expert opinion. These notes contain the key applied principals for veterinary clinicians.

**TRANSOPERATIVE PAIN**

Devising an evidence-based top-tier trans-operative pain management strategy is within the scope of any practice to achieve. The framework of effective pain management systems rests solidly on the foundation of recognition/assessment, pre-emption, and using multiple modalities. Multiple modalities allow for intervention at several different places of the nociceptive pathway, increasing effectiveness and minimizing the need for high or protracted doses of any one particular drug. It is well-established in human medicine, for example, that the use of adjunct medications will minimize the use of PCA (patient-controlled analgesia) opioids with a resultant decreased incidence of adverse effects such as nausea and constipation. In short, employing the modest use of multiple modalities is not only more effective, it avoids the over-reliance (higher doses, longer duration) of any one modality…thus limiting the likelihood of adverse effect from any modality.

The basic construct is a 4-legged stool:

**ANXIOLY蒂CS**

Anxiety contributes directly to the hyperalgesic state through cholecystokinin-mediated “nocebo” effect. A number of studies in humans support the idea that patients who are highly anxious or stressed pre-operatively experience higher pain scores post-operatively. These observations are also found in many animals studies, where restraint, social defeat, rotation – all things veterinary patients experience in the normal pre-surgical setting in order to draw blood, place catheters, etc. – contribute to hyperalgesia. Thus the first leg of a strong transoperative pain management protocol does not involve the use of analgesics in and of themselves, but anxiolytics and not just pharmacologic ones i.e. low-stress handling techniques, and the Fear-Free experience that includes the use of pheromones in addition to medications administered at home prior to transport to the clinic. A common and easy-to-administer example for cats is a 100 mg capsule of gabapentin emptied into some food (+/- mixed w/ flavored supplements such as Fotiflora and Zyklene) approx. 1 hour before placing in carrier. Once in the hospital anxiolytics are included in the pre-medication and in this modality class, clinicians may choose between phenothiazines (e.g. acepromazine), benzodiazepines (midazolam or diazepam), or alpha2 agonists (dex/medetomidine).

2 www.fearfreepets.com
OPIOIDS

Opioid receptors are distributed ubiquitously throughout the body and can be found in most central and peripheral tissues. Several opioid different receptor types and subtypes have been isolated, each with a variant effect; activation of an opioid receptor inhibits presynaptic release and postsynaptic response to excitatory neurotransmitters. Opioids in combination with anxiolytics discussed above can induce a profound sedating neurolopetanalgesic effect to the patient’s benefit. Subcutaneous absorption of most opioids in cats is highly erratic with IV and IM being the preferred routes (exception is Simbadol®, see below). Opioids in cats elicits mydriasis rather than miosis as occurs in humans and dogs.

A number of different opioid drugs are available which vary in their relative analgesic properties, pharmacokinetics, and receptor affinity, and a complete discussion of their similarities and differences are available in a number of resources. Generally speaking the trend in both human and veterinary medicine, including for cats, is to use opioid-sparing techniques to lower the frequency, dose, and schedule of opioids administration, in addition to “stepping down” insofar as possible to non-full mu agonists...i.e. from morphine, hydromorphone, and fentanyl in favor of buprenorphine and butorphanol (for which the veterinary-labeled products should not be in shortage).

Buprenorphine is a partial agonist on the mu receptor though it has greater affinity than morphine (and will displace it if given together). Unlike full mu agonists, it has a ceiling effect (beyond a certain dose it derives no additional analgesia, but little more in the way of adverse effects either). It has less sedative effect than other opioids such as hydromorphone or butorphanol. Its Tmax is slower than other opioids, up to 30 min when administered IV and an hour when administered IM. When the standard 0.3 mg/ml product (Buprenex™) is administered SC, absorption is erratic and in some cats elicits undetectable plasma levels (therefore IV and IM preferred route)⁸,⁹ A benefit of the drug in cats had been thought to be that its pKa (8.4) closely matches the pH of the feline oral mucosa (9.0), which would allow for nearly complete absorption when given buccally in that species¹⁰ with kinetics nearly identical to IV and IM administration,¹¹ and eliciting very little sedation. More recent work however (collecting non-jugular blood, demonstrates approximately 50% bioavailability¹² (about the same in humans in dogs). Simbadol® is a buprenorpine FDA-approved product labeled for 24 hours of post-surgical analgesia in cats when administered at 0.24 mg/kg SC; it can be repeated daily for 2 subsequent days. Due to the ceiling effect of buprenorphine, the product has a very wide safety margin even at 5X labeled dose (60X customary buprenorphine dose of 0.02 mg/kg).¹³ However due to the occasional modest adverse effect of behavior change and diminished appetite, the author elects to utilize at 50% dose reduction (pharmacokinetics suggest likely 24-hour efficacy at this dose as well.¹⁴

A compounded sustained-release buprenorphine product purported to last for3 days is also commercially available, although it is not FDA approved for safety and efficacy and there is no published literature to know pharmacokinetics in cats. The FDA’s Animal Drug Use Clarification Act’s statement on Extra-label Drug Use does not endorse the use of compounded medications when an equivalent FDA-Approved commercial product is on the market (in this case, another long-acting buprenorphine, in the form of Simbadol®).

Butorphanol (Torbugesic™) is a mu agonist and a kappa antagonist; its utility is greatly enhanced by its synergistic effect for both sedation and analgesia when administered with alpha-2 agonists e.g. dexmedetomidine. A common combination is the DKT dexmedetomidine, ketamine, Torbugesic™ at 0.1 ml of each per 10 lbs which renders near-anesthetic levels of immobilization; or 0.05 ml of each per 10lb which can serve as a pre-medicant or for minor procedures along with local anesthesia.

NSAID

The primary mode of action is to inhibit cyclooxygenase 2 (COX2), the enzyme that is expressed at site of inflammation and results in the production of pro-inflammatory and vasoactive prostaglandins. Also, through poorly understood mechanisms, likely by modulating multiple gene
expression pathways, it may inhibit central perception of pain. Several superior products are now labeled for use in dogs (and some in cats), making them among the most popular of pain management medications in veterinary medicine. All seem to be effective, and the main limitation of all NSAID’s revolves around the potential for adverse effects, since both COX 1 and COX 2 enzymes may be constitutive, that is, consistently present and crucial to the production of cyto-protective prostaglandins (COX1 especially in the GI tract and renal tubules, COX2 in the renal tubules). Thus the primary adverse effects of non-selective NSAID’s may include GI erosion/ulceration and nephrotoxicity. The GI and renal adverse effects can be expected to occur most commonly in higher risk patients, e.g.: hypovolemia, hypotension (including anesthetic procedures especially those not supported by intravenous fluids), pre-existing GI or renal disease, overusage, and the inappropriate combination with other NSAID’s or corticosteroids.

Meloxicam carries a relatively high dose on its label in the U.S. (0.3 mg/kg SC) which may have predisposed to incidents of acute kidney injury and renal failure in compromised cats, this prompted a “black label” advising veterinarians not to use this drug more than one dose and not orally. Used more modestly (lower doses e.g. 0.1 mg/kg) and in properly vetted, supported, and monitored patients, meloxicam has a satisfactory safety record in cats. It does have a relatively long plasma T ½ of 20 hours, compared to the COX-2 selective robenacoxib with its quite short plasma T ½ of 1.7 hours but still residing at the site of inflammation for >24 hours. Robenacoxib is labeled for pre-op use and for up to a total of 3 days through any combination of SC and PO administration.

LOCOREGIONAL ANESTHESIA
Local anesthetics were once a mainstay of pain management in veterinary medicine, and may now be one of the most under-utilized modalities. Administered locally or regionally, they are the only modality that renders complete anesthesia to a site, i.e. no transmission of nociceptive impulses as long as the drug exerts its effect. Initially used as a means of desensitizing tissues in order to “invade” tissues with scalpels; local anesthetics are enjoying a rebirth as powerful tools to prevent or reduce perioperative pain (as well as procedural and even chronic pain) and to reduce general anesthetic and concurrent analgesic (especially systemic opioid) requirements. There is no longer a reason to hold an “either-or” position; “for surgery either I use local anesthetics or I use general anesthesia”, in fact, there are many reasons to combine general and local anesthetic for surgical pain relief. A partial list of techniques, from the sublimate to the more advanced include, topical/dermal/epidermal local anesthetics for IV catheter placement (e.g. EMLA®, LMX4®, or their generic equivalents), incisional blocks, infiltrative blocks, intra-peritoneal or intra-pleural blocks, perineural blocks (e.g. brachial plexus, and radial-ulnar-medial n. "Ring" block), intra-articular blocks, dental/orofacial n. blocks, epidurals, IV Regional Anesthesia (Bier) blocks, retrobulbar blocks, intercostals blocks, transdermal blocks e.g. EMLA® (see below) and Lidoderm®.

BEST OF THE REST
Cold Compression
Long known for its pain-modifying effect in humans, recent studies affirm a similar effect in dogs. Alpha-2 agonist Medetomidine and dexmedetomidine binds opioid-like receptors on C- and A-delta fibers, especially in the central nervous system. Binding pre-synaptically, 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 and the author has found a wide use for these alpha-2 agonists in acute and peri-operative setting, though only in combination with opioids and at doses much lower than suggested by the manufacturer. One particularly novel and user-friendly utility is IV micro-doses intra- and post-
operatively, 0.25 – 1.0 mcg/kg. This may result in intravenous volumes of only 0.01 – 0.03 ml in even the largest of dogs.

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, including in the dog. Ideal sub-anesthetic ketamine plasma concentrations – eliciting the most benefit with the least adverse effect – has been reported at 2-3 mcg/ml, which can be achieved by administering ketamine IV CRI at 10 mcg/kg/min. This can be accomplished by placing 60 mg (0.6 ml of 100 mg/ml stock) ketamine in 1 L of fluids and administered at customary intra-operative rates of 10 ml/kg/hr. Post-operatively, the rate can be reduced to customary maintenance rates of 2 ml/kg/hr, which administers the ketamine CRI at 2 mcg/kg/min. A loading dose of 0.25 – 0.5 mg/kg ketamine IV is recommended prior to the initiation of the CRI in order to rapidly achieve plasma levels.

Adjunctive drugs: tramadol, gabapentin
In humans, tramadol is described as a synthetic opioid with 1/100th of the affinity for the mu receptor as morphine but a much better analgesic effect than this would predict. This is likely due to the combined effect of a highly active mu-agonist M1 metabolite and serotonin- and norepinephrine (inhibitory neurotransmitters) agonism. Cats also make the opioids M1 metabolite in some abundance with a plasma T ½ similar to humans; further there are laboratory and clinical models in both acute and OA pain demonstrating efficacy in cats. However, the drug is very bitter, and administering it orally makes it a challenge to use in this species.

Gabapentin is labeled for use as an anti-convulsant drug but is in widespread human use for its analgesic properties. While structurally similar to GABA, it is not a direct agonist, although it may have indirect effects on GABA metabolism such as increasing intracellular stores. Another leading hypothesis is that it exerts effect through interaction with the alpha-2-delta subunit of the voltage gated calcium channel. Its utility in chronic, neuropathic pain states is well-established in humans, but more recently its utility in the transoperative setting is supported by a number of systematic reviews. Pharmacokinetics in cats has been established, suggesting a TID administration schedule. Starting doses are recommended in the 3-10 mg/kg range. The primary adverse effect in dogs appears to be somnolescence (as in humans) which usually will spontaneously resolve over a few days acclimation time, but this AE not been a frequent occurrence in the author’s experience.

Overview of Osteoarthritis (OA) and Chronic Pain
Arguably the most commonly-recognized chronic-pain condition in dogs and cats, OA also presents some of the greatest challenges to treatment because of its inevitably progressive pathology, difficulty in early recognition, and need for prolonged pharmaceutical pain relief that is both effective and safe. It should be noted that the literature generally described the condition as OA in dogs and degenerative joint disease (DJD) in cats. While their pathophysiologies may be dissimilar, these proceedings will use the term OA for both species.

Osteoarthritis is an incurable condition that is characterized by degenerative changes to joints and surrounding soft tissue with accompanying degrees of pain and lameness. The etiology of OA in cats is uncertain, with less attributable to conformation (exception: hip dysplasia in Main Coons) than dogs. Cats, both young and old, appear to have a very high incidence of OA, with up to 60% of all cats have radiographic OA changes and 90% over 10 years old. Although the pathophysiology of OA may be different in dogs and cats, this means that OA in both these species can initiate early in life, far earlier (relatively speaking) than routinely in humans, and how we intervene in OA may be quite different from one life stage to another.
The earliest stages of OA begin with biochemical changes within the articular cartilage, joint fluid and surrounding joint capsule. The production of inflammatory mediators, such as prostaglandin E2, within the joint leads to the release of degradative enzymes, such as aggrecanase and matrix metalloproteinases (MMP) from chondrocytes, which then cause breakdown of the cartilage matrix. This leads to distorted cartilage mechanics and further injury to the joint. These degenerative processes become a vicious cycle, resulting in cartilage erosion, subchondral bone sclerosis, joint capsule thickening, periarticular new bone formation, and associated pain and loss of function.

OA is typically thought of as a disease of bone and cartilage. And of course, physical examination — or even just movement - often will easily elicit the clicks, pops, and thunks attributable to osteophytes and bone-on-bone crepitation. But it is instructive to point out that the pain of OA is not felt at the articular surfaces or what is left of them. Rather, the pain is largely felt in the peri-articular structures, from an inflamed synovium, when tension is placed on a fibrotic joint capsule, and when patients are asked to exert (even if just by standing or walking) weakened ligaments, tendons, and muscle. Thus OA is a disease of the entire joint organ, including dramatic synovitis, fibrosis, and atrophy…and the result is not just pain but progressive disability. Treatment has to be targeted accordingly. Complicating matters is that only in recent years has OA been affirmed to include a neuropathic component. It might be safely surmised that OA universally involves a maladaptive – even if not abjectly neuropathic - pain state in most patients. That is, the perceived pain is disproportionately greater than would be expected by the extent of pathology alone.

While there is currently no way to cure OA once it develops, it can be managed through a variety of methods, and the progression of the disease can often be attenuated. Early diagnosis and intervention has been shown to provide the most effective means of long-term management, so it is important to identify animals likely to develop OA as soon as possible. The diagnosis of OA is based on a combination of history and signalment, physical/orthopedic exam findings, and radiographs; occasionally joint fluid analysis is needed to rule out other joint diseases. Validated OA-assessment/scoring Clinical Metrology Instruments (CMI) are available in cats: FMPLI: Feline Musculoskeletal Pain Index31 www.painfreecats.org and MICAT: Montreal Instrument for Cat Arthritis Testing32

Management of OA should take a multi-modal, evidence-based medicine approach. The American Animal Hospital Association (AAHA) and the American Association of Feline Practitioners (AAFP) published updated guidelines for the treatment of OA in dogs and cats. Furthermore, there are novel therapies on the horizon that may help veterinarians target OA pain, while decreasing the potential of adverse effects that may be seen with currently available pharmaceuticals.

Recommendations for Managing OA from the 2015 AAHA/AAFP Pain Guidelines

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The Guidelines continue the trend in all branches of medicine toward evidence-based consensus statements that address key issues in clinical practice. Although not a review article, the Guidelines represent a force multiplier for the busy practitioner, consolidating in a single place current recommendations and insights from experts in pain management. The recommendations of the guidelines Task Force are evidence based insofar as possible and otherwise represent a consensus of expert opinion. These notes contain the key applied principals for veterinary clinicians.

1. Weight optimization – clearly the #1 method for preventing OA and a prime, however challenging, method for treating OA. The role of adipose tissue as a mediator of systemic inflammation, the contribution of central obesity to chronic pain in humans (doubling the risk for it), and the primacy of weight loss to diminish chronic pain signs and symptoms- is
now a settled matter. In dogs with OA, several studies illuminate the benefit of improving pain scores, mobility, and NSAID reduction with weight loss alone (even modest, i.e. only 5%). Indeed, it is probably not an overstatement to say that in an overweight patient, both the clinician and pet owner are wasting time and money on other interventions until and unless weight loss is achieved. Weight loss is best achieved through primarily caloric restriction and accompanying regular, low-impact exercise.

2. Non-steroidal anti-inflammatory drugs (NSAIDs) – There are currently no NSAIDs FDA approved for use in the management of cats with OA (DJD). In the EU, meloxicam carries a label for its indefinite use in cats for musculoskeletal pain at 0.05 mg/kg and there are several studies revealing efficacy33, 34, 35 and safety36, 37 (even in stable IRIS 1-3 CRD38 important because important because up to 2/3 of cats with DJD have concurrent CRD39) of daily low-dose (approx 0.02 mg/kg daily) for feline DJD-related pain. A more recent study using objective outcome measures demonstrated improved nighttime activity (but no improvement in force plate).40 Robenacoxib has excellent, even dramatic, long-term safety data in young healthy cats, up to 6 weeks at 10 times the labeled dose,41 and 6 months at 5 times the labeled dose.42 More recently, safety was demonstrated in stable IRIS 1 & 2 chronic kidney disease cats for 1 month at the daily labeled dose.43 Pharmacokinetics of the EP-4 receptor antagonist (a new class of non-COX-inhibiting NSAID) grapiprant has been studied in cats, and if the minimal effective concentration in dogs (164 ng/ml) also applies in cats, 2 mg/kg PO might be effective for 10 hr44 although this would be an off-label use.

3. Parenteral polysulfated glycosaminoglycans (PSGAG), in particular Adequan® which is FDA-approved for the treatment of OA in dogs. One abstract in cats demonstrates bioavailability and distribution to joints with SC administration.45 The evidence for glucosamine and chondroitin in OA remains mixed at best, although some other ingredients of oral nutraceuticals such as avocado, soybean unsaponifiables, MSM, green-lipped mussel, microlactin, and others offer in vitro suggestions for varying degrees of immunomodulating, chondroprotective, and pain-modifying effect. One recent study of a feline nutraceutical found disappointing results in a cohort of DJD patients.46

4. Diet: EPA-rich diet in dogs, DHA-rich diet in cats have shown efficacy in improving mobility in animals with OA.47

5. Note: The 2015 AAHA/AAFP Guidelines strongly emphasizes the role of low-stress handling and fear-free environment (especially in the clinic setting). For dogs and cats, a superior resource is Dr. Sophia Yin’s Low Stress Handling, Restraint and Behavior Modification of Dogs and Cats: Techniques for Developing Patients Who Love Their Visits and website, www.drsophiayin.com. For cats in particular, 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. In addition, facial pheromones are increasingly recognized for their integral role in diminishing stress, with its attendant contribution to pain. All of this is globally part of the Fear-Free experience for cats, www.fearfreepets.com.

Other modalities, while having less robust evidence in the literature, there is some evidence for the use in the management of OA:

- Pain-Modifying Analgesic Drugs (PMAD) especially gabapentin (case series reports exist for controlling other chronic/neuropathic conditions in cats e.g. Feline Hyperesthesia Syndrome48 and Feline Orofacial Pain Syndrome.49 More to the point of feline osteoarthritis, a well-designed RPCB study demonstrated efficacy in 25% of DJD cats that exhibit hypersensitization in the feet from hip osteoarthritis50, and a more recent study revealed owners observations of improvement in their DJD cats.51 Amantadine and tricyclic Antidepressants (TCA) e.g. amitriptyline may also have utility. Other drugs may find a role in the future e.g. Selective Serotonin Norepinephrine Reuptake Inhibitors e.g. duloxetine and venlafaxine.
• Acupuncture
• Myofascial Trigger Point Therapy
• Energy-based modalities e.g. Therapeutic Laser, Pulsed Electromagnetic Field (PEMF), Transcutaneous Neuromuscular Electric Stimulation (TNMES), Extracorporeal Shock-Wave Therapy (ESWT).
• Biologic Therapy e.g. Mesenchymal Stem Cell transplantation, Platelet Rich Plasma, anti-NGF monoclonal antibody (“felinization,” pilot trials complete, pivotal underway).

The relative role of these adjunct modalities remains unknown.


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11 Robertson SA, Taylor PM, Sear JW. Systemic uptake of buprenorphine by cats after oral mucosal administration. Vet Rec. May 2003;152(22):675-8
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