In the last 10 years, the veterinary profession has undergone what can only be described as a sea
change in perspectives about animal pain and pain control. In many ways the issue of pain
management in animals closely parallels that in human pediatrics, whereby the patient is non-
verbal and the clinician must rely on personal/staff observations and the reports of the patient’s
advocate (in some ways this parallel extends to human geriatrics, whereby the patients may be
once again non-verbal and a caregiver is the patient’s advocate). Thus it is that physicians have
also long struggled with the critique of under-managing pain in children\textsuperscript{1,2} the cognitively
impaired,\textsuperscript{3} and the elderly.\textsuperscript{4,5}

Under- (or un-) managed pain elicits a cascade of debilitating neuro-hormonal effects that result
in hypertension, catabolism, immunosuppression, and in what can be a terminal event, bacterial
translocation and sepsis. This is called the “stress response.” With under- (or un-) managed pain,
patients at best recover more slowly from their condition, and at worst, may develop severe, even
life-threatening complications.

However, the effect is not limited to pain of an acute nature. In addition to discomfort and
physical disability, the capacity of chronic pain to impair cognition is becoming increasingly
recognized in humans. A global summary of statistically significant findings in 42 studies of
patients with chronic musculoskeletal pain revealed that deficits of memory, attention,
psychomotor speed, and mental flexibility all can be attributed as a consequence of chronic pain,
independent of other causes.\textsuperscript{6} In animals, for all of these reasons, under-attended, under-
managed pain can become a criterion for euthanasia.

Pain itself is normal, and when physiologic it is protective. But undermanaged pain, as it
becomes extended in time and intensity, becomes maladaptive and debilitating. And the younger
the patient, the more long-term consequences of undermanaged pain because of the enhanced
plasticity of the spinal cord: hypersensitivity to thermal stimuli can be documented years after
the initial sets of painful experiences in both animals and humans.\textsuperscript{7} Thus for clinicians in a
veterinary practice, their staff, and their clients, the first step to developing an aggressive,
integrative pain management system is to internalize how dangerous and damaging
undermanaged pain is to their patients. In fact, until so convinced, stocking drugs on a shelf and
writing down protocols stands little chance of successful hospital-wide implementation.

The neuro-anatomic, physiologic, and molecular basis of nociception is a rapidly evolving field
of study. Once-simple models are now understood to be highly complex and supremely inter-
related sets of dynamics. The “Gate Control Theory”, offered in 1965 by Melzak and Wall,
proposes a feedback mechanism that controls activation of pain fibers by allowing or inhibiting
impulses through the “gate.”\textsuperscript{8} Nothing that we now understand about nociception challenges the
basic operational premise of the Gate Theory. What is new and growing is the illumination of its
details.
Nociceptors are specialized nerve fibers that have their dendritic endings in peripheral tissue, with several different subtypes identified. These nerve fibers have receptors that respond to mechanical and chemical stimuli but may be polymodal for touch, pressure, heat, cold, itch, and other sensations. When activated by the appropriate stimulus, a signal is said to be transduced, and the nerve endings depolarize. The signal is then conducted, or transmitted, electrobiochemically in an afferent direction, that is, towards the spinal cord. There, in the dorsal horn, the signal is modulated, that is either enhanced or dampened. Synapses are made with secondary neurons which ascend up the spinothalamic tract of the spinal cord to the thalamus, where another synapse occurs with tertiary neurons, which then project to the cerebral cortex where perception occurs. However, in addition to these ascending pathways to the brain are descending, inhibitory pathways; and under the proper conditions conduction can occur from the spinal cord down the peripheral nerve fibers in an anti-dromic fashion to the site of original transduction.

The fastest of the nerve fibers are the small but fully-myelinated A-beta sensory fibers which involve the sensations of touch, pressure, vibration, and proprioception. Somewhat slower are the thinly-myelinated A-delta fibers which stem from mechano-, thermo-, and nociceptors involved in sharp physiologic and acute pain. C-fibers are large and unmyelinated and hence very slow conductors of mechanoreceptors and nociceptors involved in dull, aching chronic pain. From somatic sites the cell bodies of these nerve fibers are located in the dorsal root ganglia, and from visceral sites, the sympathetic ganglia. The terminal endings of these fibers are highly tropic in the dorsal horn, with somatic A-delta and C fibers occurring in the most dorso-lateral aspect (Laminae I and II), somatic A-beta fibers terminating in the deeper Laminae II, IV, and V, and visceral A-delta and C fibers scattered throughout each of these Laminae. However, the tropism, inter-connectivity, and even phenotype of these various neurons is not static, rather the dorsal horn can exhibit dramatic plasticity, changing and altering form and function depending on a wide variety of factors: age (the younger the more plasticity), type and duration of stimulus, gender (or sexual status i.e. presence or absence of androgenic hormones), and others.

At the peripheral site of transduction, stimulus comes in the form of heat (transient vanilloid receptor 1, TRPV1), cold (cold- and menthol receptor 1, CMR1), membrane distortion, or cell damage releasing fatty acids and free ions from cell membranes. Each of these stimuli open non-specific cation channels on the peripheral endings of A-delta and C-fibers, which allows an inward Na+, K+, or Ca+ current. When a critical threshold of intracellular Na+ and/or Ca+ is reached, then activation and opening of voltage-gated cation channels occurs, which propagates depolarization afferently along the nerve fiber membrane. In addition, the free fatty acids are catalyzed by phospholipase-A2 into arachadonic acid, providing the substrate for cyclooxygenase metabolism and the initiation of the inflammatory cascade through a number of mediators e.g. prostaglandins, H+ ions, cholecystikinin, histamines, Substance P, bradykinins, leukotrienes, and many more, all highly noxious stimuli that bind to their own receptors on the nociceptor nerve ending, exacerbating or continuing the cation influx. The peripheral nerve fiber transmits its signal to the spinal cord, terminating in the dorsal horn.

In the dorsal horn, the nociceptors terminate and release various highly bioactive molecules across synapses to interneurons (also called second-order neurons). Chief among many of these in the classic model is the excitatory amino acid glutamate, which binds to AMPA receptors on the interneuron. This binding causes a sodium/potassium channel to open, allowing Na+ to flow freely through the cell membrane into cytoplasm (and K+ out into the extracellular space), which
elicits an action potential: the interneuron depolarizes and the impulse is transmitted afferently to the brain. However, as quickly as it opens, an AMPA receptor will close, unless the stimulus is sustained. If the stimulus is in fact sustained, not only will the AMPA receptor remain open, but the accumulation of intracellular Na+, will phosphorylate adjacent NMDA receptors, releasing a magnesium “plug.” The NMDA receptor is now open and free to allow calcium to inflow into the neuron, further depolarizing it for an extended period of time.\textsuperscript{12} NMDA activation is now well-established in its role of potentiating hypersensitization and neuropathic pain.\textsuperscript{13}

The second-order, or projection neurons, upon which the peripheral A- and C-fibers synapse, are characterized as wide dynamic range (WDR, sensitive to a variety of sensations, including pain) and nociceptive-specific (NS, pain-only) neurons. They ascend the spino-thalamic tract to terminate in the thalamus, with projections (via third-order neurons) to the reticular, limbic, homeostatic-control, and cortical somatosensory regions of the brain\textsuperscript{14}. Here the spatial and temporal qualities of pain become more than an unpleasant sensation, but transcends to a physical and emotional experience as well.

Inhibitory neurons, some intraspinal and some descending from the brain, synapse on the second-order neurons as well. Here the neurotransmitters are inhibitory in nature and include gamma amino butyric acid (GABA), norepinephrine (NE), certain serotonin (5-HT3), B-endosyn, and others\textsuperscript{15}. Furthermore, circulating endogenous opioids bind to kappa and delta (less so mu) receptors (closing Ca+ channels, and opening K+ channels, respectively), hyperpolarizing the cell. A basal level of interconnectivity occurs between afferent A-beta, A-delta, C-fibers, interneurons, and intra- and descending inhibitory neurons.\textsuperscript{16} Lastly, the supporting glial cells (astrocytes, microglia, oligodendrocytes) in the spinal cord, whose purpose was once thought to be merely structural in nature (providing synaptic architecture, host defense, and myelin, respectively), are now thought to be highly integrated into the pain process, particularly with regards to chronic pain.\textsuperscript{17} Recently described is the tetrapartite synapse, which includes an astrocyte, microglial cell, and pre- and post-synaptic neuronal terminal.\textsuperscript{18} A recently isolated chemokine, fractalkine, appears to be a neuron-glial cell signal, activating glially-dependent pain facilitation (in a recent rat model, blocking the one known fractalkine receptor in rats diminished the development of neuropathic pain).\textsuperscript{19} Indeed, the glia may play a primary role with regards to synaptic strength, plasticity, and sensitization in the spinal cord, which does exhibit substantial change under the influence of chronic pain.\textsuperscript{20}

Sustained nociception begins to alter the dynamic considerably, and pain can quickly move from its physiologic, protective nature to a maladaptive one. The constant presence of inflammatory and bioactive mediators at a peripheral site forms a “sensitizing soup” that creates a constant barrage of excitatory neurotransmitters in the dorsal horn. The opening of the calcium channel begins a cascade of events that in some cases becomes irreversible. An influx of calcium ion causes activation of Protein Kinase C (PKC), which in turn elicits production of nitrous oxide (NO), which then diffuses back across the synapse and through the terminal ending of the afferent nociceptor. This causes K+ channels to close and also the production of Substance P, a profoundly excitatory bioactive molecule, which then flows back across the synapse once more to bind on neurokinase (NK-1) receptors of the interneuron\textsuperscript{21} (expression of the NK-1 receptor appears to also contribute to opioid-induced hyperalgesia and tolerance\textsuperscript{22}). Not only does the interneuron stay depolarized, but a phenotypic change may be induced where it may not reset. Expression of c-fos, c-jun, and Knox-24 genes transcribe new (probably aberrant) proteins that produce permanent microstructural changes of the neuron that result in reduced firing threshold,
upregulation of central neuronal activity, downregulation of inhibitory activity, expansion of the receptive field, peripheral hypersensitivity and intensified pain responses to further stimulation.  

Furthermore, the afferent nociceptor will conduct a signal efferently, in an anti-dromic fashion. There, at the peripheral site of original stimulus, it releases Substance P and calcitonin gene-related peptide (CGRP), another highly bioactive excitatory compound, which elicits further release of inflammatory mediators and recruiting and activating other previously innocent-bystanding nociceptors, further bombarding the dorsal horn with impulses.  As the feedback loop persists, more and more cells express c-fos and other genes, Nerve Growth Factor is stimulated into production (suspected to be from glial cells), and more interconnections are made between types and locations of neurons in the spinal cord.  These interconnections are not isolated to somatosensory neurons, for they have been shown to newly express adrenoceptors which are activated by catecholamines.  Sympathetic stimulation may then result in nociception, and may in fact be central to the pathophysiology of neuropathic pain.  Moreover, neuropathic pain is associated with alterations in receptor location (more places on more axons) and sensitivity to excitatory amino acids (greater) throughout the nervous system.  Eventually, when the process of pain is located centrally (in the spinal cord) rather than at the site of the original stimulus, the pain is said to be “neuropathic” in origin.  Once neural pathways are thus sensitized, the physiologic (and physical) responses to pain may persist, even when the peripheral nerves themselves are blocked (or even transected).  Clearly, at this point, pain has become a disease unto itself.

Summary of terminology used to describe this sensitized state:
Peripheral hypersensitization: generation of an ever-present “sensitizing soup” of inflammatory mediators (prostaglandins, bradykinin, cytokines, neuropeptides), activation of quiescent (silent/sleeping) bystanding nociceptors from non-injured tissue, reduction of threshold in normally-high threshold nociceptors.

Central hypersensitization: increase in the excitability of neurons in dorsal horn of spinal cord, cumulative depolarization (“wind up”) amplifying the neuronal activity in dorsal horn, generation of Nerve Growth Factor which promotes interconnections between formerly segregated types and locations of neurons, expression of new receptors, and phenotypic modification of nerve function.

Neuropathic pain: the extension of hypersensitization which is the initiation of transmitting a pain impulse (spontaneous depolarization) in the absence of noxious stimuli, or out of proportion to it.

In both acute and chronic pain, other non-neural peripheral tissues are not exempt from physical changes as well.  Reflex muscular spasms are not only themselves painful, they may compromise vascular supply, and the resulting ischemia can result in release hydrogen ions and ATP, which are also highly sensitizing agents.  This can result in altered, maladaptive conformation and gait, leading to abnormal stresses on ligament, tendon, cartilage, as well as and hyperirritable bands of contracted muscle (myofascial trigger points, TrP).

Glial cells (astrocytes, microglia, oligodendrocytes) in the spinal cord, whose purpose was once thought to be merely structural and macrophage-like in nature (providing synaptic architecture, host defense, and myelin, respectively), are now thought to be highly integrated into the pain process, particularly with regards to chronic pain.  Recently described is the tetrapartite synapse, which includes an astrocyte, microglial cell, and pre- and post-synaptic neuronal
terminal. A recently isolated chemokine, fractalkine, appears to be a neuron-glial cell signal, activating glially-dependent pain facilitation (in a recent rat model, blocking the one known fractalkine receptor in rats diminished the development of neuropathic pain). Indeed, the glia may play a primary role with regards to synaptic strength, plasticity, and sensitization in the spinal cord, which does exhibit substantial change under the influence of chronic pain.

There is no one moment when pain is transformed from physiologic to “acute” to “chronic” to “hyperesthetic” to “allodynic” to “neuropathic”. Rather it exists on a continuum with a high degree of biologic variation from patient to patient. There is also recent evidence that anxiety in the acute setting, mediated by cholecystokinin rather than mobilization of the hypothalamic-pituitary-adrenal axis, plays a major role in creating a chronic, hyperalgesic state.

Historically, the focus of analgesia has been to diminish transduction (e.g. local anesthesia, anti-inflammatories) and perception (e.g. opioids), and indeed these remain crucial components of a multi modal approach to pain management. The most exciting area of attention today however is in the dorsal horn, by enhancement of inhibitory modulation of nociception and interrupting the feedback loop that results in exaggerated pain responses and perception. As greater understandings emerge of the molecular and physiologic bases of pain emerges, new opportunities for intervention also emerge.

---

11 Levine JD et al, Peptides and the primary afferent nociceptor, J Neurosci 1993; 13:2272-2286
19 Shan S, New evidence for the involvement of spinal fractalkine receptor in pain facilitation and spinal glial activation in rat model of monoarthritis, Pain 129(1-2) May 2007: 64-75
24 ibid
27 Ramer MS et al. causes and consequences of sympathetic basket formation in dorsal root ganglia. Pain 1999; 6:S111-120
33 Shan S, New evidence for the involvement of spinal fractalkine receptor in pain facilitation and spinal glial activation in rat model of monoarthritis, Pain 129(1-2) May 2007: 64-75
It is clear that non-steroidal anti-inflammatory drugs will likely remain the most commonly utilized modality to manage pain. They are highly effective, commonly available, licensed for use in dogs, and generally quite safe…and because inflammation is one of the underlying physiologic mechanisms by which pain is generated, their mechanism of action puts this class of drug as among the most important tools in the toolbox. At the same time, however, like other classes of drugs, NSAIDs do carry the potential for adverse effects that might range from the mild to the catastrophic.

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,\(^1\) 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 head to head studies now emerging may help to reveal objective differences if they are present. 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. COX1-sparing NSAIDS should have a dramatically diminished GI toxicity profile, but will maintain their risk for nephrotoxicity. Rarely and on an idiosyncratic basis, hepatotoxicity may occur.

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. Notable in this last category is client use of aspirin in their pets, which may be unbeknownst to the clinician unless specifically queried in a thorough history. Unique to aspirin, this NSAID produces a cyto-protective lipoxin through the COX pathway;\(^2\) thus when COX is inhibited through the use of another, concurrently-given NSAID, the potential for GI toxicity is considerably enhanced. The relative roles and molecular dynamics of COX1, COX2, and a possible new variant COX3, is still being elucidated and the “final word” on the optimal COX-selective or –sparing effect in order to maximize effectiveness and to limit toxicity, is yet to be heard. Acetaminophen may elicit some of its analgesic effects by inhibiting the COX3 variant, and recent studies suggest that it may also inhibit COX2-mediated production of PGE2.\(^3\)

Lipooxygenase also metabolizes arachadonic acid, but instead of prostaglandins the byproducts are leukotrienes, which are potent attractors of PMN’s and promote their adherence to endothelium. One commercial veterinary NSAID, tepoxalin, inhibits LOX as well as balanced
COX enzymes. In any use of NSAID’s, the potential for adverse effects needs to be made clear to pet owners, and for any extended use, regular metabolic monitoring should be performed.

The long-term use of NSAID’s may increase the chances of adverse effects, in particular GI and nephrotoxicity, but the evidence is beginning to suggest that whether a patient experiences an AE is less dependent on longevity of use than it is on biologic predisposition to occur, and improper use. One study looking at 19 cases of NSAID-induced GI perforation in dogs established that >90% of these patients were given concurrent corticosteroids or another NSAID (or no washout period between two different NSAID’s), or were given higher than recommended doses for extended periods of time. To wit, the American Gastroenterological Association reports that 44% of respondents in a survey reported personally using higher than the recommended doses of NSAID, and up to 40% of pet owners may give their pets’ aspirin at one time or another. Thus the veterinary clinician must be strident in their query of pet owners about other medications in the pet’s history, and in their instructions about chronic usage. In general, a 5-day washout between NSAID’s is recommended, and 10 days specifically for aspirin. Strict monitoring of clinical status and renal and hepatic values becomes a vital part of long-term NSAID usage.

NSAID’s have been used, although cautiously, in patients with stable chronic renal failure; a rule of thumb is to multiply the dosing interval by the factor of the serum creatinine to account for decreased renal clearance (for example if it is a Q 24 hour medication and the creatinine is 3.0 mg/dl, then the modified interval would be 24 x 3 = every 72 hours or once every 3 days). Due to the reno-protective effect (vasodilation) of COX2-mediated metabolites of arachadonic acid, it is possible that patients with documented CRD would be candidates to receive more balanced NSAID’s. Patients receiving an ACE-I for protein-losing nephropathy or cardiovascular disease are at risk for adverse effects; in this case, the NSAID may blunt the effect of the ACE-I, and the ACE-I can potentiate the risk renal damage. Close monitoring of all of these patients, using the least effective doses, is warranted, and they are possibly more suited for balanced COX inhibitors. Where possible, the use of other modalities may allow lower NSAID doses which may in turn increase the safety profile, although there is no data to support this construct.

In all cases of NSAID use, the practice must consistently and reproducibly educate clients regarding the potential adverse effects of this class of drug. More than ¾ of individuals reporting adverse NSAID events to the FDA hotline feel that their veterinarian did not inform them adequately of possible side effects, and/or failed to give the client the drug information sheets provided by the pharmaceutical company. Acetaminophen appears to have weak COX-1 and COX-2 inhibition, but may inhibit a centrally-expressed COX-3 and a partial COX1 (PCOX-1) enzymes, mediating an analgesic effect by dulling the pain sensory system. Acetaminophen is contraindicated in cats and in patients with liver disease, and should be used with caution in dogs due to limited experience and diminished metabolism when compared to humans.

Tips For NSAID Use:

In the surgical setting, whether to administer NSAID pre- or post-operatively is a clinical decision. The edge in efficacy goes to pre-operative use in both humans and dogs. Level 1 evidence evidence suggest safety of pre-operative NSAID in humans, as do multiple RCT’s
(Level 2 evidence) in healthy dogs vis-à-vis renal function even with moderate intra-operative hypotension. However, it is axiomatic that patients undergoing general anesthesia should have the benefit of intravenous fluid support, which would further increase the safety margin of NSAID use even pre-operatively. One unpublished case series of cats undergoing de-sexing not receiving IVF did result in a number of patients experiencing acute renal failure with only 1 or 2 doses of various NSAID. Customarily, NSAID are given during the expected course of post-operative inflammation, as little as 3 days for minor or elective procedures, up to several weeks for more major surgery.

Minimizing the Risks of NSAID: 8 Easy Steps

1. Complete medication history, including specific queries re: aspirin, other NSAIDs by brand name, “steroids”, “cortisone”, nutritional supplements (some have COX-inhibiting mechanisms, some may actually contain aspirin itself). Other medications:
   a. Highly protein-bound drugs e.g. phenobarbital, digoxin, cyclosporine, chemotherapy agents
   b. furosemide and ACE-inhibitors
   c. Potentially nephrotoxic drugs e.g. aminoglycosides, cisplatin
2. Patient selection – caution or avoid NSAID with existing or anticipated
   a. Low flow states such as hypotension, hypovolemia, dehydration (and all anesthetic procedures should have IV fluid support, blood pressure monitoring), and CHF
   b. renal, cardiac, or hepatic dysfunction
3. Verbal and written client instructions to avoid the medications describe in #1 above, and to discontinue and alert the hospital at the first sign of an AE (see #4)
4. Recognize the earliest signs of AE and withdraw immediately: most often decreased appetite or an episode of vomiting, usually within 2-4 weeks but can occur at any time
5. Laboratory monitoring, frequency depending on the risk factor of the patient
   a. Ideally within first month of initiating, then Q 6 months thereafter in low-risk patients
   b. For higher risk patients, frequency Q 2 – 4 months
6. Use NSAID-sparing strategies (multi-modal approach to pain management) to find the lowest effective dose over time, if the patient requires extended use
7. Washout aspirin, meloxicam (10 days), other NSAIDs, or corticosteroids (3 days) if possible prior to initiating NSAID
8. Gastroprotectants if necessary (to treat suspected gastropathy or to prevent in the event no washout can occur): proton-pump inhibitors are superior to H2 antagonists, and misoprostol (Cytotec®, a PGE2 analogue) is considered the drug of choice in humans although sucralfate (Carafate®) can also be helpful

Summary of literature findings, including Systematic Reviews on veterinary NSAIDs, with specific regards to toxicities and treatment of osteoarthritis in dogs:

Hepatotoxicity: Rare: 1.4 cases per 10,000 dogs (0.052%), usually between 2-4 weeks of initiating; elevated liver enzymes not a risk factor. “FDA ADE reports suggest that hepatic
toxicity can occur with any veterinary NSAID, and there are no reports identifying a particular
NSAID as having an increased risk of idiosyncratic hepatic toxicity in dogs.” (KuKanich 2012)
“No extensive studies (properly designed i.e. crossover, randomized) of clinical dogs using all
available veterinary NSAIDs; but existing studies suggestive that the COX-1 sparing NSAIDs
produce a lower frequency of GI lesions” (Kukanich 2012); while at the same time “…studies
suggest that the more highly COX2-selective inhibitors may actually produce more adverse
effects when underlying gastric damage is present.” (Goodman 2009)

Gastrointestinal toxicity

- #1 clinical sign associated w GI toxicity: vomiting, followed by inappetance (Stanton
  1989, Lascelles 2005, Neiger 2003); however it is possible for erosions and ulcers to be
  silent and occur prior any prior clinical signs. (Stanton 1989, Wooten 2010)
- #1 risk factors for GI perforations are excessive dose and concurrent with other NSAIDs
  or corticosteroids, or combinations of these. (Lascelles 2005)
- Signs of GI toxicity usually emerge within 2-4 weeks but can occur at any at any point
during administration. (Hampshire 2004, Robertson 2008)
- Veterinarians are generally very poor at communicating NSAID toxicity risk factors to
  pet owners or even handing out client information sheets with NSAID prescriptions.
  (Hampshire 2004).
- 22,200 NSAID incidents reported to the ASPCA Animal Poison Control Center between
  2005-10; the most common drugs cited was ibuprofen, followed by aspirin, naproxen,
  whether accidental ingestion or owners administering the drug.
- With veterinary NSAID’s, “No study has comprehensively compared the AE profile or
  efficacy of the currently produced NSAIDs in head to head trials. Similarly, none of the
  studies have produced consistent results to indicate any of the veterinary- approved
  NSAIDs as being associated with more or less adverse effects in clinical patients.”
  (KuKanich 2012)
- Pre-operative administration in dogs is superior in efficacy to post-operative. (Lascelles,
  1998), consistent with results of multiple studies performed in humans
- Nephrotoxicity: Administered pre-anesthetically in healthy dogs with controlled modest
  hypotension, no adverse affect on renal function was detected by the various outcomes
  measured such as serum BUN and creatinine concentrations, urine GGT:creatinine ratio,
  urinalysis, and glomerular filtration rate via scintigraphy. (Ko 2000, Bostrom 2002,
  Lobetti 2000, Crandell 2004, Bostrom 2006). “However, these are much less sensitive
  indicators than renal blood flow, altered distribution of blood flow through renal cortex,
  urine sodium clearance (which have not been extensively studied).” (KuKanich 2012).
  The renal safety of NSAID in healthy patients undergoing anesthesia is also established
  in humans. Similar studies have not been in cats (undergoing anesthesia), but one feline
  study revealed no alteration in glomerular filtration rate, as measured by iohexol
  clearance, after 5 days of oral meloxicam.
- Tissue healing: highly COX-2 selective NSAIDs have demonstrated delayed bone
  healing in rabbit and rodent models, and 1 study in dogs demonstrated delayed TPLO
  fracture repair with long-term use of NSAID. However, normal tissue healing is rapidly
  restored when the NSAID is withdrawn; a meta-analysis in humans reported no
  increased risk of nonunion with NSAID exposure when only the highest-quality studies
  were assessed; and of deracoxib, carprofen, and firocoxib, 299 dogs received one of
these NSAIDs in the FDA approval process and none reported to have delayed fracture healing or nonunion fractures.\textsuperscript{43} Note: A systematic review in humans undergoing intestinal resection/anastomosis does reveal an increased risk of leakage at the anastomotic site with the use of COX-2 selective NSAIDs,\textsuperscript{44} but this effect has not been studied in animals.

- **Veterinary NSAID’s** studied for chronic use (28 days to 1 year) demonstrated satisfactory safety profiles in dogs, with discontinuation of use due to adverse effects in the 3-5\% range (Innes 2010). While a similar systematic review has not been performed in cats, the 6-month safety of reduced-dose meloxicam (0.01-0.03 mg/kg/day) has been reported,\textsuperscript{45} and the results of one retrospective study suggested that a long-term maintenance low-dose of 0.02 mg/kg/day of meloxicam can be safely administered to cats older than 7 years even if they have chronic kidney disease, provided their overall clinical status is stable (and may actually slow the progression of CKD in some cats).\textsuperscript{46} A new feline COX-2 selective NSAID, robenacoxib, revealed no toxicities at 6X and 10X labeled daily dose for the duration of the 6-week study.\textsuperscript{47}

- Under outcomes measured, carprofen may demonstrate chondroprotective effects in dogs.\textsuperscript{48,49,50,51} Studies of other veterinary NSAIDs, and in cats, are still needed.

- In two studies of long-term use of NSAID for canine osteoarthritis, clinical scores continued to improve during the entire duration of the study. (6 months carprofen, Autefage 2010\textsuperscript{52}; 1 year firocoxib, Autefage 2012\textsuperscript{53})

- Therefore with regards to long-term use of veterinary NSAIDs in the treatment of canine osteoarthritis, “… a number of lines of evidence suggest the potential theoretical benefits of continuous versus intermittent NSAID analgesic therapy for osteoarthritis.” (Innes 2010)

New in NSAID’s

- In 2015, the FDA designated a new “piprant” class of “non-COX-inhibiting NSAID.” It represents a new targeted inhibition of strictly the EP4 receptor of PGE2, with the hope of a prospectively wider safety margin than historical COX-inhibiting NSAID. The first drug in this class, grapiprant, is expected to be approved in the U.S. in 2016. Safety data reveals minimal ADE at 15x expected labeled dose administered for 9 months.\textsuperscript{54}

- robenacoxib (Onsior\textsuperscript{®})\textsuperscript{1}: available in Europe, and approved by the FDA for post-operative pain in cats in the U.S. in 2011, this unique COX-2 selective\textsuperscript{55,56} NSAID has a short plasma half-life in this species (1.7 H), yet accumulates in inflammatory exudates for up to 24 hours.\textsuperscript{57,58} This novel “tissue-specific” character appears to fulfill the promise to provide both safety and efficacy in cats, and in fact, while approved only for 3 days post-operatively, a 6-week trial in cats revealed the drug to be well-tolerated even at 3X and 5X the labeled dose.\textsuperscript{59} In a recent study of cats undergoing ovariohysterectomy, robenacoxib appeared to elicit superior post-operative pain control than meloxicam.\textsuperscript{60} Note: robenacoxib has been approved for use in dogs in Europe with a similar profile as found in cats, but is not imminently available in the U.S.

- RevitaCAM\textsuperscript{™} (Abbott Animal Health), an oral transmucosal meloxicam spray, has been approved in the UK for acute and chronic musculoskeletal pain in dogs and cats, and may be in the pipeline for U.S. release as well. It is a 5 mg/ml solution, with the dosage being 0.2 mg/kg for the first dose followed by 0.1 mg/kg/d thereafter; the specially-
designed dispensary glass bottle (3 different concentrations sizes) dispenses a metered dose/spray per pump. The U.S. formulation of this product, OroCAM™, was withdrawn from the market in 2013.

- mavacoxib (Trocoxil®, Europe only) - sustained-release NSAID approved for chronic pain in dogs. A 2010 search for literature yielded an abstract on the pharmacokinetics of the drug² but no information on efficacy; the manufacturer reports 30 days after 1 dose.⁶

- nitronaproxen (Naproxcinod®, Europe only for humans) is a cyclooxygenase-inhibiting nitric oxide-donating drug (CINOD) in Phase III trials that appears to have the analgesic efficacy of the parent NSAID but with a greatly reduced incidence of negative side effects because of the positive effects of the NO.⁸ Naproxcinod has been shown to control the pain of osteoarthritis in humans.⁶²

---

⁵ Gastroenterological News, 05/22/04
⁷ Gaynor, JS, Clinician’s Update, NSAID’s: Liver & Kidney Disease in the Osteoarthritis Patient Dec 2006:2-4
⁸ Atkins, CE, Clinician’s Update, Canine Heart Disease and NSAID’s, June 2007:2-4
⁹ Hampshire VA, Adverse drug event reports at the US FDA Center for Veterinary Medicine, JAVMA 225:533-536 2004
¹¹ Plumb’s Veterinary Handbook, Plumb DC, 2005
¹⁴ Lee A, Cooper MC, Craig JC, Knight JF, Keneally JP. Effects of nonsteroidal anti-inflammatory drugs on postoperative renal function in adults with normal renal function. Cochrane Database Syst Rev. 2007 Apr 18;(2)


Food & Drug Administration, Freedom of Information www.fda.gov


A limiting factor of many analgesic medications, including opioids, is a relatively short duration of action. Extending opioid duration of action to last several days provides several unique therapeutic advantages:

1. Eliminates plasma concentration peak/troughs encountered with repeated parenteral dosing.
2. Steady state of opioid can be achieved at plasma levels sufficient to elicit analgesia without the use of intravenous constant rate infusion or transdermal patches.
3. Eliminates multiple injections to administer opioid periodically throughout at 24-hour period.
4. Eliminates staffing requirements to reliably administer an opioid through a 24-hour period, further eliminating compliance and variability issues. (This feature in laboratory animals provides, by extension, consistency for the study model.

Thus there is an increasing interest in sustained-release and/or long-acting parenteral opioid formulations and technologies in humans and animals, several of which have been investigated: some adopted from human use, some from compounding pharmacies, and one of which has recently received FDA approval in dogs. The applications are to be found both in clinical patients and in research animals (where the stress of handling to administer B-QID drugs, and 24-hour staffing requirements to do so, is considered confounding to study models).

A number of different technologies have been explored and utilized to achieve long-acting opioid effect:
In animals, the efficacy, durability, and tolerability of liposome-encapsulated (LE) hydromorphone has been demonstrated in dogs, with adequate serum levels up to 4 days and superior analgesic effect 12 hours post-ovariohysterectomy compared to subcutaneous morphine. This same formulation, route, and dose demonstrated favorable pharmacokinetics and tolerability in rhesus macaques when compared to subcutaneous or intravenous hydromorphone. Similar studies with LE oxymorphone and hydromorphone have been performed in laboratory animals demonstrating durability, tolerability, and effectiveness (rhesus macaques and rodents). However liposomes are highly labile, with limited shelf-life and expensive to produce. Currently, no commercial LE-opioid product is available on the market.

Fentanyl is a short-acting opioid conventionally administered via constant-rate intravenous infusion. It has also been available in the U.S. as a transdermal patch formulation since 2005 (Duragesic®), labeled in humans for breakthrough cancer pain, and has been studied (and used off-label) in dogs, cats, and rabbits for post-operative and other kinds of pain. Study results have demonstrated utility in these species but also wide variability in serum concentrations, even when application of the patch is standardized. Add the variables of patch location (trunk, vs. limb, with different dermatologic characteristics and temperature), body condition (amount of adipose tissue in skin), and even how well and properly the patch stays secured to the skin (or not), and the reproducibility of reliable plasma levels from patient to patient should be called well into question. An additional concern with this technology is human exposure to the reservoir, which is not only easily divertible for illicit use, but also potentially dangerous including death when ingested (and to which children are particularly susceptible; 10 fatal cases have been reported since 1997). Indeed, one study examining the residual fentanyl in the patch after attachment to dogs for 72 hours concluded that it was significant and could easily lead to human intoxication (note: the study did not analyze remnant fentanyl actually located on the dogs’ skin, but it might be presumed that exposure to humans could also occur via skin-to-skin contact). While Duragesic patches maintain some traction in veterinary medicine, and may be particularly indicated for...
specific patients, the plasma variability, and prospective liability, has caused it to carry
less popularity in veterinary medicine than it once did.

Fentanyl patches also come in a non-reservoir, gel matrix patch (Matrifén® and
generics), indicated for chronic pain. The fentanyl in these products is more difficult to
divert for illicit use, but the liability issue remains similar to Duragesic® and insofar as
the author is aware, no PK or PD studies on this type of patch have been published in
animals.

More recently, a long-acting fentanyl product with a novel delivery system was approved
in dogs for post-operative pain (Recuvyra®, Elanco). This product makes use of patented
Metered Dose Transdermal Spray (MDTS) technology (Medistend™, already in human
use to deliver estrogen and testosterone supplementation, contraception, and other
compounds) and is labeled to provide plasma levels of fentanyl adequate to provide
analgesia for 4 days. The solution is highly concentrated fentanyl, 50 mg/ml, and is
applied at a dose of 1.2 mg/lb (2.7 mg/kg) to healthy skin at the dorsal scapular region 2-
4 hours before surgery; staff are advised to wear personal protective equipment and the
patient is to wait a minimum of 2 minutes before returned to a holding area; the area of
application should not be touched for 5 minutes. During this time, a penetration enhancer
(octyl salcylate, commonly used in sunscreen) drives the fentanyl into the stratum
corneum, 15 layers of dead cells in a lipid matrix. A depot of fentanyl resides within the
lipid matrix and it slowly releases into circulation by passive diffusion along a
concentration gradient.

Several peer-reviewed articles have explored the pharmacokinetic and pharmacodynamic
properties of Recuvyra™. Analgesic plasma levels of fentanyl (1 ng/ml) are
reached within 3 hours, with a Cmax of 13 hours. Interestingly, the drug has
demonstrated “Flip flop” kinetics: the rate of absorption is slower than the rate of
elimination.

Skin to skin contact does not lead to human exposure, in fact the administration model
appears not to work in human skin. However, skin to mucous membrane exposure (i.e.
touching the area and then touching to mouth, eyes, etc.) is possible. Therefore it is
advised that the application area not be touched for 72 hours, and to segregate the patient
from children during that time. The adverse effects are reported to be those typical of
any opioid, and reversible if necessary with the opioid antagonist naloxone 0.04 mg/kg
IM; however due to the short duration of naloxone and the long-duration of the drug,
sequential re-administration will be required, every 1-3 H. Further, naloxone at
customary doses can be expected to reverse both the adverse and analgesic effects; recall
however that low-dose naloxone (0.004 mg/kg) has been shown to reverse the adverse
effect, while maintaining the analgesic effect, of opioids; however such use of naloxone
has not been evaluated with Recuvyra™. Off-label, nalmefene may antagonize the
fentanyl for longer than naloxone (extrapolating from human doses, 0.25 μg/kg - 30
μg/kg; an oral formulation of nalmefene is commercially available, used for alcohol
addiction in humans, but no data exists in dogs).
Buprenorphine is recently available for humans as a transdermal patch (Transtec®, BuTrans®, Buprederm®). Rabbits and rodents achieved rapid plasma levels (1-24 hours) with peak analgesic activity with the tail-flick and writhing model at 3-4 hours and sustained for 72 hours of the study. However in one feline study using a 35 mcg/h patch, plasma levels were negligible and there were no changes in thermal thresholds. The experience in dogs is somewhat better. In one canine study utilizing a 70 mcg/h patch resulted in sustained plasma concentrations of 0.7-1.8 ng/ml within 36 hours of application. Another canine study utilizing a 52.5 mcg/h found peak plasma levels of 1.54 ng/ml and analgesic efficacy to be non-inferior to IV buprenorphine in mechanical & thermal thresholds within 36 hours of application and lasting until the patch was removed; however there was some inconsistency as 3 of the 10 dogs recorded negligible plasma levels. An additional clinical canine study found the 70 mcg/kg patch to be non-inferior to SC buprenorphine post-ovariohysterectomy.

Buprenorphine is also available in a compounded (non-FDA approved) sustained-release formulation (Zoopharm) administered subcutaneously. The technology utilizes a biodegradable polymer which is dissolved in a biocompatible solvent. Upon SC injection, the polymer precipitates or coagulates upon contact with aqueous body fluid to form an implant matrix, from which the active drug is gradually release as it degrades. Several such biodegradable polymers are in common commercial use, such as N-Methyl-2-Pyrrolidone (NMP, which degrades via the tricarboxyclic acid cycle into CO2 and water), and Triactin (TCN, glycerin and acetic acid). These polymers are in common use with cosmetics, various medical beads and implants, and several other products familiar to veterinarians including doxycycline-impregnated percutaneous treatments and absorbable sutures.

Unpublished PK data in dogs report plasma levels adequate for analgesia for over 72 hours, but there are anecdotal reports of prolonged and in some cases dramatic sedation especially at the higher end of the dosage range (0.27 mg/kg SC) in larger dogs. Unpublished PK data in cats superior maintenance of plasma levels adequate for analgesia over 3 days when compared to repeated OTM dosing. One published PD study in cats found SR buprenorphine to be non-inferior to Q 12 H OTM dosing for three days post-ovariohysterectomy, with minimal adverse effects when administered at 0.12 mg/kg SC. Similar positive outcomes have been observed in unpublished studies with non-human primates and rodents, and in one published rat study.

In July 2014, a new veterinary formulation of buprenorphine was FDA-approved in the United States and introduced into the marketplace (Simbadol®, Abbott). At 1.8 mg/ml it is 6 X more concentrated than the human commercial product Buprenex® (0.3 mg/ml). It is labeled for post-surgical pain in cats, a 24-hours duration with one injection at 0.24 mcg/kg SC; it can be given daily for up to 3 days. The labeled dose is 0.24 mg/kg, approximately 10x histor previously recommended. The operating premise is that the ceiling effect of buprenorphine limits adverse effects while allowing the extended analgesic duration. Each 10 ml vial allows for approximately 15 doses. The shelf-life of an unopened vial is 21 months, and once opened, 28 days.
Long-acting opioids remain an area of active research, and new products may be finding their way into the marketplace, and possibly FDA-approved, in the coming years.

27 Veterinary Information Network Anesthesia & Analgesia Message Boards, International Veterinary Academy of Pain Management Listserv Forum
31 Wildlife Pharmaceuticals, internal research.
Outside the realm of NSAID and opioid exist a broad range of medications that exert an analgesic effect, or otherwise modify and protect against pain, by manipulating various targets along the nociceptive pathway.

**ALPHA-2 AGONIST**

Alpha-2 and opioid receptors are co-located on central nociceptors, and use of the two drug classes together is highly synergistic for sedation and analgesia. Alpha-2 binding pre-synaptically reduces NE production is reduced and sedation occurs; binding post-synaptically, analgesia is produced. 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 although central perfusion is maintained. It has a versatile dosing profile where low (5 mcg/kg) and even micro-doses (0.25 – 1 mcg/kg, resulting in volumes as low as 0.01-0.03 ml even in larger dogs) with opioids are clinically useful and minimize the cardiovascular effects. Be mindful that these lower doses will shorten the duration of the drug, and the analgesic effects may wane prior to the sedative effects. The safety and pain modifying effect of dexmedetomidine constant rate infusions have been described.¹

**KETAMINE**

A phencyclidine dissociative anesthetic ketamine exerts a pain-modifying effect predominantly as potent NMDA-receptor antagonist. Ketamine binds to its 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 Ca²⁺ ion influx and dampening secondary intracellular signaling cascades. Hence it is unlikely (and has not been shown) to be truly analgesic in nature. Rather, subanesthetic ketamine constant rate infusion (CRI) has been shown convincingly in humans to have pain-preventive, anti-hyperalgesic, anti-allodynic effects¹²,¹³,¹⁴ and existing studies in the dog appear support a similar clinical effect in dogs¹⁸,¹⁹ (not yet studied in a feline surgical model). The International Veterinary Academy of Pain Management has adopted a position that the pain-modifying effects and safety warrant the consideration of subanesthetic ketamine as part of a multi-modal approach to transoperative pain management, especially in patients with risk factors that may dispose them to exaggerated or maladaptive pain states.

**INTRAVENOUS LIDOCAINE**

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)¹¹ 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, 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. 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.

Some investigators discourage the use of IVL in cats due to negative cardiovascular effects, but anecdotally has been utilized in clinical practice. Systemic, intravenous infusion of lidocaine has also been shown to elicit a sustained effect on neuropathic pain in humans, and may have a specific point of action in the brain.

Note: Alpha-2 agonists, systemic lidocaine, and ketamine CRI are sedating and can be profoundly anesthetic-sparing especially in combination with opioids. If administered during anesthesia, induction doses and maintenance vaporizers should be adjusted downward accordingly, and can often be at 1% or less. The drug concentrations and fluid rates may be adjusted to fit the needs of the individual patients. Rate calculators are available on www.vin.com (Library/Calculators) and www.vasg.org/resources & support material.

TRAMADOL

In humans tramadol is known to exert its pain-modifying effect through two metabolites; one enhances inhibitory neurotransmitters (serotonin, norepinephrine), and the other (0-desmethyltramadol, or “M1”) metabolite is a weak opioid (1/100th the mu-receptor affinity of morphine). However, tramadol has a very short half-life (1.7 hours) in the dog and it appears that dogs produce very little of the M1 opioid metabolite. Nevertheless pharmacodynamic studies in dogs have demonstrated the anesthetic-sparing and pain-modifying effect of parenteral tramadol, Convincing evidence for a pain-modifying effect of oral tramadol remains elusive at this time. Furthermore, PK studies in dogs reveal that not only are plasma levels much lower following oral administration than in humans, sequential dosing for several days leads to dramatic reductions of those plasma levels (suggesting saturation of GI active transport sites, increased metabolism, more robust first-pass effect, or a combination). One study of oral tramadol reports a statistically significant increase of mechanical threshold levels, but only at the 5- and 6-hour time point. One study does find oral tramadol effective as part of a multi-modal analgesic protocol to control cancer pain, but others have found it (not unsurprisingly) inferior as a solo agent to multi-modal analgesic approaches to control post-operative pain. The short half-life of the drug suggests up to a Q-6 hour treatment regime, but one unpublished abstract on the effectiveness of tramadol administered once daily in canine osteoarthritis appears encouraging. In contradistinction to dogs, cats do produce the mu-agonist M1 metabolite, and a pain-modifying effect has been demonstrated in both a thermal threshold and clinical surgical model, as well as a case series of use of oral tramadol.
in a flavored compounded form (the drug is otherwise quite bitter). Toxicity and safety data are lacking in both dogs and cats.

**GABAPENTIN**

Gabapentin is an anti-convulsant that analgesic properties predominantly by down-regulating voltage-dependent calcium channels but other mechanisms probably exist as well (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). Because of its effectiveness and tolerability, it is in widespread use for humans with neuropathic and other maladaptive pain conditions, and this suggests, along with published case reports, a strong rationale for the utilization of gabapentin in analogous conditions experienced by dogs and cats. The utility of gabapentin for osteoarthritis in demonstrable in rodent models, one canine study suggests a disease-modifying effect in experimental osteoarthritis, but no clinical studies have been published investigating gabapentin canine OA. However, case reports exist of successful use in treating non-OA neuropathic pain conditions in both dogs and cats. In cats, one unpublished study is reported to demonstrate a benefit of gabapentin in naturally-occurring osteoarthritis, in addition to a case series of chronic musculoskeletal pain.

Systematic reviews in humans support safety and benefit of transoperative oral gabapentin for post-surgical pain. The evidence in dogs and cats for efficacy in acute pain currently is disappointing, but one case series utilizes gabapentin in cats with acute traumatic musculoskeletal injuries. Pharmacokinetic studies in dogs reveal that it may have a half-life of 3-4 hours in the dog, suggesting a TID administration schedule although anecdotally BID appears to be useful. The primary adverse effect in dogs appears to be somnolescence (as in humans) which usually will spontaneously resolve over a few days acclimation time. For chronic pain dosing, a general consensus is that doses are initiated at 3 mg/kg and gradually tapered upwards as the patient can tolerate to a target dose range of 20 mg/kg. In the perioperative setting, dose based on the experience in humans is 10 mg/kg.

**AMANTADINE**

Amantadine exerts a pain-modifying effect as an NMDA receptor antagonist and remains a research focus for chronic pain (but not specifically osteoarthritis) in humans. One study does demonstrate utility as an adjunct to NSAID in dogs with refractory osteoarthritis. Toxicity and kinetic studies have been performed in humans and cats but not in dogs. Amantadine dosing range is 3-5 mg/kg orally once daily.

**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 dogs there exists only a single case report of utilizing amitriptyline for neuropathic musculoskeletal...
pain, and in cats the experience in idiopathic cystitis\textsuperscript{82} (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. Customary doses of amitriptyline are 1-2 mg/kg BID in the cat and dog, but a recent review article suggests 3-4 mg/kg based on its PK profile in these species.\textsuperscript{83}

**SS(N)RI’s**

These compounds exert their effect by increasing serotonin +/- norepinephrine in the synaptic cleft. At least one SSNRI, duloxetine, has a chronic pain label in humans, but bioavailability is poor in dogs\textsuperscript{84} and clinical efficacy is lacking.

Note: many drugs and compounds enhance monoamines and/or serotonin and caution should be undertaken when or if used in combination. Examples include: tramadol, TCA’s including amitriptyline and clomipramine, SS(N)RI’s, amantadine, metoclopropamide, selegiline, amitraz, mirtazepine

**ACETAMINOPHEN**

Acetaminophen is contraindicated in cats. In dogs, several older studies reveal a pain-modifying effect in orthopedic surgery,\textsuperscript{85} \textsuperscript{86} and pharmacokinetic data has been reported.\textsuperscript{87} The literature does not appear to support that the dog has any special proclivity towards hepatotoxicity.

**MAROPITANT**

Maropitant is a central antiemetic through blockade of Substance-P to the NK-1 receptor, which is also involved in pain processing. The true pain-modifying effect in dogs remains uncertain despite one study in dogs revealing an anesthetic-sparing effect\textsuperscript{88} and another a non-inferior effect to morphine in an ovariohysterectomy model.\textsuperscript{89}

**BISPHOSPHONATES**

Administered by IV infusion, the class of drug exerts anti-osteoclast activity and can contribute to pain relief in dogs with bone cancer.\textsuperscript{90}

**CORTICOSTEROIDS**

Corticosteroids are not analgesic in and of themselves, but likely exerts an indirect pain-modifying effect through by reducing inflammation. Its utility as an analgesic therapy in dogs and cats has not been reported, although several studies of intra-articular corticosteroids suggest possible chondroprotection.\textsuperscript{91} \textsuperscript{92} \textsuperscript{93} \textsuperscript{94}

**POLYSULFATED GLYCOSAMINOGLYCANS**

Parenterally-administered PSGAG products have regulatory approval as safe and effective chondroprotectants, supported by independent studies.\textsuperscript{95} \textsuperscript{96} \textsuperscript{97}

**NEUTRACEUTICALS AND OTHER ORAL SUPPLEMENTS**

Oral nutritional supplements represent a wide spectrum of compounds as single agents or in combinations. Evidence for a pain-modifying effect of these various products remains mixed at this time although some display some encouraging data may exist for some. If
neutraceuticals or herbal supplements are made part of a treatment plan, the Task Force suggests mindfulness towards: quality control, potential drug interactions with other medications (for example, some OTC joint products contain aspirin), and ingredients derived from endangered species.

2 Ketamine: Does Life Begin at 40? IASP Pain Clinical Updates, Carr DB, ed. XV:3, June 2007
5 Subramaniam K et al. Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. Anesth Analg. 2004 Aug;99(2):482-95
11 McCarthy GC, Megalla SA, Habib AS. Impact of intravenous lidocaine infusion on postoperative analgesia and recovery from surgery: a systematic review of randomized controlled trials. Drugs. 2010 Jun 18;70(9):1149-63
16 Tsai TY, Chang SK, Chou PY, Yeh LS. Comparison of the postoperative effects between lidocaine infusion, meloxicam, and their combination in dogs undergoing ovariohysterectomy. Vet Anaesth Analg. 2013 Jul 9.
60 Cashmore RG, Harcourt-Brown TR, Freeman PM, Jeffery ND, Granger N. Clinical diagnosis and treatment of suspected neuropathic pain in three dogs. Aust Vet J. 2009 Jan-Feb;87(1):45-50
62 Troncy E, personal communication 2013
77 Lascelles BDX, Gaynor J, Smith ES. Evaluation of Amantadine as Part of a Multimodal Analgesic Regimen for the Alleviation of Refractory Canine Osteoarthritis Pain, WORLDSmall Animal Veterinary Association World Congress Proceedings, 2007
92 Pelletier JP, Martel-Pelletier J. In vivo protective effects of prophylactic treatment with tiaprofenic acid or intrarticular corticosteroids on osteoarthritic lesions in the experimental dog model. J Rheumatol Suppl. 1991 Feb;27:127-30
2015 AAHA/AAFP PAIN MANAGEMENT GUIDELINES:
WHAT IT MEANS FOR YOUR PRACTICE
Mark E. Epstein, DVM, Dipl. ABVP C/F, CVPP
TotalBond Veterinary Hospitals
Gastonia, Charlotte NC
International Veterinary Academy of Pain Management

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:

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:

ANXIOLYRICS

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\(^1\) and pheromones in addition to tranquilizers/sedatives. In this modality class, clinicians may choose between phenothiazines (e.g. acepromazine), benzodiazepines (midazolam or diazepam), or alpha2 agonists (dex/medetomidine).

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. The proposed mechanism includes opioid receptor coupling with the membrane-associated G protein; this leads to decreased intracellular formation of cAMP which diminishes calcium channel phosphorylation (closing off the channel) and opens potassium channels enhancing potassium influx. The resulting effect is hyperpolarization of the neuron and blockade of Substance P release. Nociceptive transmission is thus greatly impeded.\(^7\) Opioids in combination with anxiolytics discussed above can induce a profound sedating neurolopetanalgesic effect to the patient’s benefit.

Similarly, a number of different opioid drugs are available which vary in their relative potency and receptor affinity, and a complete discussion of their similarities and differences are available in a number of resources. Briefly, however, of the pure mu agonists, morphine remains the prototype in widest use; it has no ceiling effect on analgesia or respiratory depression, elicits histamine release, and causes vomiting at low doses (higher doses, IV doses, and chronic use do not elicit vomiting, presumptively by interaction with mu receptors in the antiemetic center\(^8\)). Cats lack glucuronate metabolism, resulting in minimal production of the analgesic M6G metabolite\(^9\), therefore morphine may not be the ideal opioid for use in this species. Oxymorphone (Numorphan\(^\text{®}\)) and hydromorphone (Dilaudid\(^\text{®}\)) do not elicit histamine release (therefore may be wiser choice in cases of hypovolemia e.g. trauma, dehydration), and nausea may be less pronounced, but they have a much shorter duration of action than morphine; also, hydromorphone in particular is implicated in episodes of hyperthermia in cats.\(^{10}\) Fentanyl in a transdermal patch (Duragesic\(^\text{®}\)) remains useful in veterinary medicine though a number of studies have demonstrated wide kinetic variability in veterinary patients due to species, body condition score, body temperature, surgical procedure, where and how well the patch is placed, etc.\(^{11,12}\) A long-acting veterinary transdermal preparation, labeled for 4 days post-surgical pain relief in dogs, is now commercially available (Recuvyr\(^\text{™}\)). Buprenorphine is a partial agonist on the mu receptor though it has greater affinity than morphine (and will displace it if given together). A great benefit of the drug in veterinary medicine is that its pKa (8.4) closely matches the pH of the feline oral mucosa (9.0), which allows for nearly complete absorption when given buccally in that species\(^{13}\), with kinetics nearly identical to IV and IM administration,\(^{14}\) and eliciting very little sedation. Simbadol\(^\text{®}\) is a buprenorphine

FDA-approved product labeled for 24 hours of post-surgical analgesia in cats; a compounded sustained-release buprenorphine product purported to last for 3 days is also commercially available, although it is not FDA approved for safety and efficacy. Butorphanol is a mu agonist and a kappa antagonist; its very short duration of action in the dog (approx. 30-40 min) makes it a poor choice for an analgesic in this species, though used parenterally it has utility as an adjunct with other medications such as alpha-2 agonists. Tramadol (Ultram®), in contradistinction to humans, does not appear to have any opioid activity in the dog (although it does in cats).

Opioids for all their effectiveness may create clinical challenges as well. In the acute setting, opioid-induced dysphoria, hyperalgesia, and respiratory depression may be encountered; recognizing and having strategies for counteracting their signs will minimize the complications that they present.

**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 head to head studies now emerging may help to reveal objective differences if they are present. 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. COX1-sparing NSAIDS should have a dramatically diminished GI toxicity profile, but will maintain their risk for nephrotoxicity. Rarely and on an idiosyncratic basis, hepatotoxicity may occur. 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. Notable in this last category is client use of aspirin in their pets, which may be unknownst to the clinician unless specifically queried in a thorough history. Unique to aspirin, this NSAID produces a cyto-protective lipoxin through the COX pathway, thus when COX is inhibited through the use of another, concurrently-given NSAID, the potential for GI toxicity is considerably enhanced. The relative roles and molecular dynamics of COX1, COX2, and a possible new variant COX3, is still being elucidated and the “final word” on the optimal COX-selective or –sparing effect in order to maximize effectiveness and to limit toxicity, is yet to be heard. Acetaminophen may elicit some of its analgesic effects by inhibiting the COX3 variant, and recent studies suggest that it may also inhibit COX2-mediated production of PGE2. Lipooxygenase also metabolizes arachadonic acid, but instead of prostaglandins the byproducts are leukotrienes, which are potent attractors of PMN’s and promote their adherence to endothelium. A veterinary NSAID, tepoxalin (Zubrin®) that inhibits LOX as well as balanced COX enzymes is no longer
commercially available. In any use of NSAID’s, the potential for adverse effects needs to be made clear to pet owners, and for any extended use, regular metabolic monitoring should be performed.

**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 sublime 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,\(^{21}\) including in the dog.\(^ {22}\) 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.\(^ {23}\) 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 (Ultram®) is described as a synthetic opioid with 1/100\(^{th}\) 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 M1 metabolite and serotonin- and norepinephrine (inhibitory neurotransmitters) agonism. However, recent work demonstrates that it appears to have a very short half-life (1.7 hours) in the dog,\(^ {24}\) and it appears that dogs produce very little of the M1 opioid metabolite.\(^ {25}\) Only recently have some studies demonstrated the probable clinical usefulness of parenteral tramadol in dogs,\(^ {26}, 27, 28, 29\) but none so far with the oral formulation. The unfavorable PK profile of oral tramadol in dogs, and the lack of confirmatory data about its pain-modifying effect, should lend skepticism about its use as an analgesic in this species. Any pain-modifying effect of tramadol is likely derived from it serotonin- and norepinephrine-enhancing activity, therefore tramadol should only cautiously be used with other serotoninergic medications such as tricyclic antidepressants.

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.\(^ {30}\) Its utility in chronic, neuropathic pain states is well-established in humans,\(^ {31}\) but more recently its utility in the transoperative setting is supported by a number of systematic reviews.\(^ {32}, 33, 34, 35, 36, 37\) Pharmacokinetic studies in dogs reveal that it may have a half-life of 3-4 hours in the dog\(^ {38}\), 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 somnolence (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.
CHRONIC PAIN

Several “Disability” indexes and “Quality of Life” scoring systems are available and can be used to semi-quantify patient comfort, mobility, and abilities, e.g.
CODI:  Cincinnati Orthopedic Disability Index
HRQL:  Health Related Quality of Life

Degenerative Joint Disease & Osteoarthritis
OVERVIEW:  Arguably the most commonly-recognized chronic-pain condition in dogs and cats, DJD also presents some of the greatest challenges to treatment because of its inevitably progressive pathology, and difficulty in early recognition. DJD is the inclusive term that includes OA. Interestingly, cats appear to have a much higher incidence than dogs, with reports of 60-90% of all cats, including young ones, affected with radiographic DJD changes (which implies it may have a different pathophysiology than the DJD encountered in dogs). Complicating matters is that only in recent years has the question been asked (in humans and rodent models): does DJD lead to a neuropathic component? The answer seems to be yes, at least in some patients (for example, in 25% of humans with stifle OA patients). Indeed it might be safely surmised that DJD & OA specifically eventually does create 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.

DJD is typically envisioned 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 is not felt at the articular surfaces or what is left of them. Rather, the pain is 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.

As difficult a job exists to devise an EVBM-approach to surgical pain, the challenge is many-fold times that with a multi-modal plan for osteoarthritis, which progresses in such variable ways, and with such variable responses to different interventions from patient to patient. Add in a paucity of properly-designed literature in dogs and cats vis-à-vis treatment, and widely divergent client (and veterinarian) values, and a real difficulty exists to formulate a standard approach.

However, it is possible to point out where the literature is strongest, and the neurophysiological/pharmacologic rationale the most compelling, and structure a plan around those modalities.

Weight optimization – clearly the #1 method for preventing DJD and a prime, however challenging, method for treating DJD. 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 osteoarthritis, 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.

NSAID – An abundance of literature in humans, dogs, and cats, as well as two Systematic Reviews of treatments for canine osteoarthritis therapy (which constitute Level 1 Evidence), reveal this class of drug to be, by far, the most predictably effective therapy. A number of studies now appear to point to the effectiveness as well as the safety of long-term NSAID in cats.

Parenteral polysulfated glycosaminoglycans (PSGAG), in particular Adequan®, which is FDA-approved for the treatment of OA in dogs with bioavailability and efficacy supported by a number of independent studies. Another injectable glycosaminoglycan for horses, pentosan polysulfate (PPS, Cartrophen®), also has some evidence for benefit in canine OA although not available in the U.S. 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, microactin, and others offer suggestions for varying degrees of immunomodulating, chondroprotective, and pain-modifying effect.

Diet: EPA-rich diet in dogs, DHA-rich diet in cats

Controlled Exercise: Long understood to elicit analgesia in humans, this non-pharmacologic modality is now considered equally important in dogs. The pain-modifying effect likely emerges from a convergence of benefits, including but not limited to: gate-theory-mediated analgesia, production of endogenous opioids, micostability of joint due to strengthened soft-tissue/peri-articular structures. Controlled exercise can be facilitated through a formal Physical Rehab program, and at-home programs can also be designed for the individual pet.

Other modalities, while having less robust evidence in the literature, are supported for use in the management of DJD

Acupuncture

Pain-modifying Analgesic Drugs (PMAD) especially gabapentin and amantadine, possibly Tricyclic Antidepressants (TCA) e.g. amitriptyline. Other drugs may find a role in the future e.g. Selective Serotonin Norepinephrine Reuptake inhibitors e.g. venlafaxine, and acetaminophen (+/- opioid e.g. codeine, hydrocodone) (DOGS ONLY).

Myofascial Trigger Point Therapy

Energy-based modalities e.g. Therapeutic Laser, Transcutaneous Neuromuscular Electric Stimulation (TNMES), Extracorporeal Shock-Wave Therapy (ESWT).

Biologic Therapy e.g. Mesenchymal Stem Cell transplantation, Platelet Rich Plasma.
4 Subramaniam K, Subramaniam B, Steinbrook RA. Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. Aesth Analg 2004 Aug;99(2):482-95
11 Egger CM Plasma fentanyl concentrations in awake cats and cats undergoing anesthesia and ovariohysterectomy using transdermal administration, Vet Anaesth Analg 2003 30:229-36
14 Robertson SA, Taylor PM, Sear JW. Systemic uptake of buprenorphine by cats after oral mucosal administration. Vet Rec. May 2003;152(22):675-8
15 Carr, DB (Ed.) Opioid Side Effects, In: IASP Pain Clinical Updates, April 2007 XV:2
21 Ketamine: Does Life Begin at 40? IASP Pain Clinical Updates, Carr DB, ed. XV:3, June 2007
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). 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.¹

Local anesthetic drugs are extremely effective, inexpensive and easy to use. When local anesthetic drugs are administered, pain impulses originating in the periphery are blocked and prevented from reaching the central nervous system. This blockade has several positive consequences:

- The sensation of pain is alleviated or even eliminated for the duration of the block. Local anesthetic drugs work by blocking sodium channels in nerve membranes. Decreased permeability to sodium slows the rate of depolarization so that the threshold potential is not achieved and an action potential is not propagated, thus the pain impulse is not propagated. Local anesthetics bind more readily to ‘open’ channels, thus rapidly firing nerves are more susceptible to blockade.
- The likelihood that ‘wind-up’ or hypersensitization will occur is greatly decreased because the portion of the pain pathway called ‘transmission’ is blocked. Transmission involves the conductance of pain impulses from the peripheral nociceptors to the dorsal horn neurons in the spinal cord. The neurons in the dorsal horn are responsible for central sensitization. By blocking input to these neurons, central sensitization (or ‘wind up’) is less likely to occur.
- The analgesia allows the patient to be maintained under a lighter plane of anesthesia and this makes the anesthetic episode safer for the patient. In fact, local anesthetic drugs decrease the minimum alveolar concentration (MAC) of all anesthetic gases.
- Local anesthesia to a surgical site permits comfortable awakening from anesthesia, creating a sparing effect of other analgesic medications (thus decreasing the likelihood of their adverse drug effects
- Local anesthetics have been associated with fewer exaggerated, sustained (i.e. maladaptive, neuropathic) pain states.
- Lastly, local anesthetics are recognized to have many beneficial effects beyond blocking nerve conduction; broad anti-inflammatory effects (reduced production of eicosanoids, thromboxane, leukotriene, histamine, and inflammatory cytokines; and scavenging of oxygen free radicals) and even antimicrobial, antifungal and antiviral effects.² ³
Furthermore, local anesthetic blocks are extremely cost effective and can increase profits to the clinic.

**Commonly used local anesthetic drugs in veterinary medicine include**

- **Lidocaine**
  - Onset of action: rapid (less than 5 minutes)
  - Duration of action: 60-120 minutes
  - Dose 2-6 mg/kg (use the lower end of the dose in cats)
  - Convulsive dose in dogs: 11-20 mg/kg
  - Lethal dose in dogs: 16-28 mg/kg
  - ‘Toxic dose’ in cats reported as 6-10 mg/kg
  - The general recommendation for clinical use is ≤ 6 mg/kg in the dog and ≤ 3-4 mg/kg in the cat.

- **Bupivacaine**
  - Onset of action: approximately 5-10 minutes after injection (up to 20 minutes)
  - Duration of action: 4 to 6 hours
  - Dose 1-2 –(4) mg/kg (use the lower end of the dose in cats)
  - Toxic dose in dogs: 5-11 mg/kg or potentially any amount given IV
  - Data is mostly anecdotal in the cat but the general feeling is that 3 mg/kg is the toxic dose.
  - The general recommendation for clinical use is ≤ 2 mg/kg in the dog and ≤ 1 mg/kg in the cat.

**Adverse events caused by local anesthetic drugs:** extremely rare but can include any of the following:

- Local tissue effects – swelling, bleeding, inflammation, ‘tingling’? (unknown if this occurs in animals). A commonly held misconception is that local anesthetics impair wound healing – although they can powerfully inhibit the inflammatory component of cellular tissue influx, there is no evidence to support impaired wound healing. Both bupivacaine and ropivacaine have been implicated in myotoxicity, although it appears that this has not been listed as a complication in most human studies where these drugs were infused for 24 – 36 hours postoperatively into a wound bed. With proper technique and avoidance of needle induced trauma, local anesthetics can be used without the fear of negative effects on healing.
- Anaphylaxis – rare, more common with esters (but still rare)
- Central nervous system – muscle tremors, seizure, coma
  - At lower concentrations, depression of inhibitory neurons occurs and can cause cerebral excitation, which may lead to seizures. At higher concentrations, profound CNS depression with subsequent coma, respiratory arrest and death can occur. The latter is more likely following IV boluses of large doses.
- Cardiovascular system – the myocardial conduction system is sensitive to local anesthetics and IV boluses can result in cardiovascular collapse. ONLY LIDOCAINE CAN BE ADMINISTERED IV (and never with epinephrine).
- Methemoglobinemia – rare, but can occur in cats.
• Motor and autonomic nerves are also blocked by local anesthetics, and so motor weakness and vasodilation may occur with certain techniques. Blockade of essential nerve function, like that of phrenic nerve, or high epidural blocks, should be avoided. Motor weakness or paralysis of limbs, from spinal or major nerve trunk blockade is transient and as long as the patient is protected from injury and undue stress, should not be of consequence.

LOCOREGIONAL APPLICATIONS

The locality of administration is often limited only by the clinician’s ability to learn various utilities and anatomic landmarks; few are outside the scope of any clinician to master. They include, but are not limited to local line or paraincisional blocks, regional blocks such as carpal ring, dental nerve, and intercostal blocks, subcutaneous diffusion blocks, testicular blocks, intra-articular blocks, and epidurals. Facet blocks are commonly used in humans though not yet described in veterinary medicine, although recently a paravertebral block was described for dogs.

Commonly used local anesthetic blocks in veterinary medicine

For many of the blocks listed below, a suggested volume of drug is listed based on the amount of drug that can physically be injected into the site. However, with all blocks, the total dose that the patient can receive should be calculated and the cumulative dose (add up the dose or volume injected for each block) should not exceed this total dose.

1. Cavity block
Pre-closure of celiotomy, the designated amount of local is injected into the abdominal cavity, or mixed into a final lavage without suctioning out. The safety (as long as no active venous bleeding) and efficacy of this simple technique has been demonstrated in multiple veterinary studies. Intra-peritoneal infusion of LA has been utilized for painful abdominal conditions such as pancreatitis, bile and septic peritonitis. Intrathoracic injection of local anesthetic can be utilized for indwelling chest tubes, other painful intra-pleural conditions, and even to relieve the pain of pancreatitis (afferent innervation of the cranial peritoneum courses through the chest before entering the spinal cord).

2. Transdermal/cutaneous
Commercial transdermal products are extremely useful in facilitating catheter placement and for minor procedures involving the dermis and epidermis. A lidocaine/prilocaine ointment formulation (EMLA®, also comes as a generic) is placed on a shaved area and covered with a non-porous wrap (foil or cellophane). In humans it is recommended to have the product in place for 45 minutes to achieve full affect, but in the author’s experience 15-20 minutes appears sufficient in dogs and cats. Penetration depth of analgesia has been reported to be time dependent and from 2-6 mm. Commercial 5% lidocaine patches (Lidoderm®) provides post-operative wound paraincisional analgesia. However, Lidoderm® patches in fact are manufactured and labeled for post-herpetic neuralgia (Shingles), a very common form of chronic, neuropathic pain in humans. The pharmacokinetics of this product has been investigated in dogs and cats, with minimal systemic absorption noted. The adhesive patches can be cut formed to the desired size and shape, for example on either side of an incision. One cautionary note is that an entire patch contains 700 mg of lidocaine, obviously a dose that would be toxic if ingested; therefore adequate
precautions need to be taken to ensure the patient is unable to access the patch. Studies in humans with moderate-severe stifle osteoarthritis reveal significant reduction in pain intensity after 2-week use of Lidoderm® patches, and pain relief similar to that achieved by oral NSAID. Their potential for use in animals for chronic pain conditions (e.g. osteoarthritis, osteomyelitis, osteosarcoma) remains plausible but no applications are described in the veterinary literature.

3. ‘Field’ block
Blocking the ‘field’ of surgery. Local anesthetic drugs can be administered around the incision or directly into the incision. It is not true that lidocaine in an incision causes a delay in healing. Savvas et al (2008) reported that a subcutaneous incisional midline block prior to celiotomy provided superior pain relief, compared with postoperative bupivacaine or saline infiltration in dogs having a variety of abdominal surgeries. These authors used a dose of 2 mg/kg of 0.25% bupivacaine. Carpenter et al (2004) compared the effects of intraperitoneal bupivacaine with that of saline and lidocaine in dogs having ovariohysterectomy and found that the bupivacaine treated dogs received less supplemental analgesia and had improved pain scores. These authors used a higher than commonly recommended dose of bupivacaine (4.4 mg kg⁻¹ 0.75% bupivacaine diluted with saline to a volume of 0.88 ml/kg), in the cranial intraperitoneal space with an additional 2 ml of 0.75% bupivacaine on the incision prior to closure. Tobias et al 2006 did not find a benefit to a preoperative subcutaneous infiltration of 1.1 mg/kg bupivacaine in cats having ovariohysterectomy, but this dose is low compared to other studies. In another study in cats, lidocaine was infused subcutaneously, dripped on the ovarian pedicles and on the linea prior to closure, and the requirement for supplemental anesthetic doses of ketamine were significantly reduced, compared to cats treated with equivalent volumes of saline. The total dose of lidocaine used was 5 mg/kg. Results of veterinary studies suggest that incisional and intraperitoneal use of local anesthetics can spare opioid requirements and improve pain scores, and this is supported by multiple studies of similar techniques in humans having laparotomy.

4. Indwelling diffusion/wound catheter block (sort of a long term field block)
A relatively new strategy to extend the duration of local anesthesia may markedly help patients with moderate to severe surgical injury. Implantation of a catheter into the surgical wound site prior to closure allows repeated or continuous infusion of local anesthetics into the affected area. Indwelling, or ‘soaker’, catheters should be considered for large wounds or incisions that may be difficult to block or that may require continuous or intermittent delivery of drug for several days. The catheters can be buried in or near incisions and local anesthetic infused through the catheter to provide more long-term analgesia. Very useful for surgeries with large incisions, eg: amputations, mastectomies, etc. Local anesthetic drugs can be infused via a pump or administered by intermittent injection (eg, q 6-8 hour injections of bupivicaine). The catheter is generally removed in 48-96 hours. In humans, relatively costly FDA approved catheters are used. For veterinary use, two moderately priced types are commercially available. The basic form is a soft pliable catheter with tiny holes along the end that is implanted; functioning somewhat like a garden “soaker hose”. Utility, efficacy, and safety has been demonstrated in humans (Liu et al, 2006) and dogs. reported. Duration is commonly 2 days, and the veterinary utility includes: limb amputation, ear canal ablation, intercostal and sternal thoracotomy, celiotomy, and major soft tissue tumor excision, with excellent results and few complications.

5. Oral blocks (Figure 1): Blocks listed below will cause unilateral desensitization from the site of injection rostrally to midline.
Maxillary or infraorbital nerve block, cranial approach: The infraorbital nerve exits the infraorbital foramen, which can be palpated as a depression in the buccal mucosa dorsal to the distal root of the maxillary 3rd premolar (just cranial to the root of the 4th premolar or carnassial tooth in the area where the gingiva on the maxillary bone and the gingiva on the lip join together). Block the nerve by injecting local anesthetic under the gingiva just rostral to the foramen or insert the tip of the needle into the infraorbital canal and inject. Injecting into the foramen insures more caudal spread of the block but is not necessary if the oral surgery site is rostral to the foramen. Also, the foramen can be difficult to locate or to enter in small dogs and cats & infusion rostral to the canal is still useful as there will be some caudal migration of the local anesthetic into the canal. A vessel runs with this nerve so aspirate, then slowly infuse drug (0.1 to 1.0 ml).

Mandibular nerve block, extraoral approach: The mandibular foramen or the mandibular nerve can often be palpated on the lingual side of the mandible just rostral to the angle of the mandible and just caudal to the last molar in approximately the middle 1/3rd of the mandible (as measured from top to bottom). Regardless of whether or not the nerve or foramen can be palpated (often difficult to palpate in very small patients), the landmarks described above will be utilized for deposition of local anesthetic drug. The nerve ENTERS the mandible at the mandibular foramen and cannot be blocked between the mandibular foramen and the mental foramen. Landmarks are the same as those described above but the approach is from the outside, through the skin at the angle of the mandible. This technique is easier than the intraoral technique in cats and in some small dogs. Pass the needle through the skin along the medial aspect of the mandible with the needle perpendicular to the mandibular cortical bone, to the level of the foramen (again, aiming for a site just caudal to the last molar on the lingual side of the mandible). With a finger in the oral cavity the needle can be felt under the gingiva. When the site near the mandibular foramen is reached, aspirate and inject the local anesthetic drug (0.2-2.0 mls).

6. Testicular block
Isolate body of testicles, inject lidocaine or bupivacaine into the body of the testicle until you feel ‘pressure’, generally ½-2 ml per testicle in dogs and cats; the drug will migrate up spermatic cord. For incision directly over testicle, continue infiltrating as the needle exits the testicular body to block the skin and subcutaneous tissue. For incision in other location, inject local anesthetic in skin and subcutaneous tissue at site of incision.

7. Ovarian block
The mesovarium can be infiltrated with lidocaine, generally 0.5 mls per side in small dog up to 1-2 mls/side in large dog (up to 5 mg/kg total). Elevate ovary, infiltrate mesovarium, elevate
opposite ovary, infiltrate mesovarium, remove first ovary, remove the second ovary and proceed with the ovariohysterectomy.

8. **Digit or paw block (Figure 2)**

The three point (or four point) technique: Locate the carpus and the accessory carpal pad, inject 0.1-0.3 mls subcutaneously at three sites: 1) medial to the accessory carpal pad (blocks median nerve and palmar branch of the ulnar nerve); 2) lateral and proximal to the accessory carpal pad (blocks dorsal branch of the ulnar nerve); and 3) on the dorsal-medial portion of the carpus (blocks superficial branches of the radial nerve).

The Ring block: Similar to three point block but use a subcutaneous ‘line’ of local anesthetic all the way across the dorsum of the paw and another ‘line’ all the way across the ventrum of the paw to provide a ‘ring’ of local anesthesia that desensitizes the nerves described above.

9. **Intercostal block**

Inject local anesthetic in the tissues caudal to the proximal portion of the ribs. Inject local anesthetic in 2-3 rib spaces in front of and 2-3 rib spaces behind the area that needs to be desensitized.

10. **Brachial plexus block**

Locate the point of the shoulder, the first rib and the transverse processes of the cervical vertebrae, insert a 2-3 inch needle (an epidural needle will work) at the point of the shoulder to the point where the tip of the needle is even with the first rib. Keep the needle horizontal during placement so that the tip does not enter the thoracic cavity. Aspirate, then inject 1/3 of the local anesthetic (2 mg/kg bupivicaine diluted with saline to a total 1 ml solution per 4.5 kg body weight) at this site, slowly withdraw the needle to the middle of the area to be blocked, aspirate and inject 1/3 of the local anesthetic. Withdraw the needle to a site just before it exits the skin, aspirate and inject the remaining 1/3 of the local anesthetic.

11. **Sacro-coccygeal block**

![Fig 2 - Diagram of a cat’s distal forelimb showing the locations for placement of local anesthesia for desensitization of the digits. Diagram used with permission from Tranquilli WJ, Grimm, KA, Lamont LA. Pain Management for the Small Animal Practitioner. Teton New Media Jackson, WY, 2000.](image-url)
Indicated for perineal, tail procedures including: relief of urinary obstruction, perineal urethrostomy, anal sacculectomy, peri-anal mass removal, tail amputation. The patient is placed in sternal recumbency, palpate the space between the sacrum and the 1st coccygeal vertebra while dorsoflexing tail (between Cx 1-2 also acceptable). Clip & prep, Use a 25ga 1” needle to penetrate the skin at midline. Direct the needle at a 30 to 45 degree angle and continue through the interarcuate ligament. There may be a palpable “pop” when the ligament is penetrated; as the needle is advanced, there is no resistance upon entering the epidural space. If bone is encountered, keep the needle in the skin and slightly angle the needle cranially or caudally off the bone until the space is entered. The needle feels more firmly seated once the ligament is penetrated than it does in the subcutaneous tissues. Inject 0.5 ml of 2% lidocaine or 0.5% bupivacaine; there should be no resistance.

12. Retrobulbar block\(^{22, 23}\)

With a 1 ½” 22g needle, enter suborbital above the lateral 1/3 aspect of the zygomatic arch. Direct caudo-medially to come up underneath and behind the globe. Aspirate and inject the local anesthetic.

References for technique descriptions:

5 Hofmeister EH, Kent M, Read M. Paravertebral block for forelimb anesthesia in the dog—an anatomic study Vet Anaesth & Analg 2007, 34:139-142
10 Wahlgren CF, Quiding H. Depth of cutaneous analgesia after application of a eutectic mixture of the local anesthetics lidocaine and prilocaine (EMLA cream). J Am Acad Dermatol. 2000 Apr;42(4):584-8