

Applications of Pain Management Advancements in Primary Care

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Current Concepts: Neurophysiology of Pain and Delivery of Pain Care

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. A 1993 evaluation of a veterinary teaching hospital surgical caseload revealed only 40% of patients that had undergone highly invasive, painful procedures (including orthopedic repair, thoracotomy, and intervertebral disc decompression) received any sort of pain control, and then only based on clinical signs.¹ Looking at more routine elective procedures, a 1996 evaluation revealed that in primary care, no more than 17% of patients undergoing ovariohysterectomy received any sort of pain control, and of those, the vast majority received just one or two injections.² Veterinarians at all levels continue to cite a variety of reasons for their reluctance to use or prescribe peri-operative analgesics.³

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^{4,5} the cognitively impaired,⁶ and the elderly.^{7,8}

A landmark study in human neonatology illustrates the issue. Up until the early 1990's a standard anesthetic/analgesic protocol in neonates undergoing thoracotomy for repair of congenital cardiac defects included the use of halothane followed by intravenous morphine and diazepam post-operatively administered periodically on an as-needed basis. In a prospective trial, such procedures elicited a mortality rate of 27%. When the peri-operative protocol was modified to include sufentanil (a potent, rapid-acting, highly soluble pure mu agonist) by constant rate infusion, the mortality rate reduced to 0%.⁹

Through this stark example we see the clinical effects of under- (or un-) managed pain. It 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.¹⁰ In animals, for all of these reasons, under-attended, under-managed pain can become a criterion for euthanasia.

The case for aggressive pain management in veterinary medicine exists in two spheres. One is ethical, in which case we may say that our patients deserve the freedom from discomfort.¹¹ However it is a curiosity that for all of veterinary medicine's well-known capacity for compassion, it is only recently that we include pain management as an integral part of patient care, and indeed veterinarians across the spectrum of age, training, work environment, geography, and species-interest still do not always agree on what our ethical responsibilities exactly are with regards to the relief of pain (and, one might add to complicate the discussion, fear, stress, and distress). This we must leave to the philosophers and sociologists, though the more pain management is integrated into the care of animals, the more it will become a cultural shift to the norm.

The other case for aggressive pain management exists in the sphere of clinical effect and scientific evidence. 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.¹² 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 next obstacle that must be overcome is that of patient adaptation and human bias. In the study of neonates cited above, why did doctors and nurses in the NICU give morphine to some babies and not others, and at certain times and not others? Largely – but not exclusively - because their biases had them expecting certain behaviors to tell them their patients were in pain (crying, for example; but most premature infants do not have that capacity). Veterinarians and staff – and pet owners! - suffer the same prejudice.¹³ Animals' adaptive behaviors, and our own preconceived notions about what animals "should" be doing if they were in pain, have led us down a path of self-deception.¹⁴ The consequence is a tendency to underappreciate and under-manage pain in animals.¹⁵ A recent study reveals that in cats, behavioral alterations persist for several days at home after ovariohysterectomy or castration.¹⁶ In order to fully embrace a comprehensive, integrative pain management system for a practice, all stake holders must consciously dismiss the arrogant thought that we can know with confidence the level of pain our patients are experiencing. With doctors and staff this can be done with one or a series of staff meetings, and a consensus can be developed. With clients, it is one pet owner at a time, to wit: "He has trouble getting up in the morning, and can't go up the stairs at all any more, but he's not in pain."

Another common obstacle is the reluctance to use new medications or modalities, for lack of familiarity, or for fear of adverse effects. The following sessions will attempt to alleviate some of these concerns, and with regards to the potential for adverse effects, one must always measure that type of risk against the well-established risk of undermanaged pain. There are numerous resources available to the practitioner looking to leverage ever-more aggressive pain management on behalf of their patients; some are listed below. Health care providers in both human and veterinary medicine have also expressed a distaste of having to stock and manage controlled drugs; fortunately AAHA publishes an excellent guide on managing controlled drugs¹⁷.

Lastly a practice must develop its pain management systems. This must include written protocols (AAHA Standard PM8), and scoring pain as the 4th vital sign after T, P, and R (MA23, PM1). In its Pain Management Standards, the American Animal Hospital Association (AAHA) provides an extremely useful template from which to articulate a practice's philosophy, policies, and methodologies of patient care in this area.¹⁸ The protocols should include the key elements of being pre-emptive and multi-modal in nature; the author recommends as a rule of thumb that a minimum of 3 separate interventions be in place for a patient's painful condition. Client education material must be handy and utilized. In the exam room, discussions with the pet owner about pain management must accompany every conversation involving surgery, trauma, and the aging pet. Computer systems should automatically link standard pain management protocols to procedures and estimates. The following sessions will illuminate the enormous pain management arsenal that veterinarians can leverage on behalf of their patients; but in order to fully grasp their roles and potentials, one must grasp the fundamentals of pain neurophysiology.

Neurophysiology of Pain: Current Concepts

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."¹⁹ 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*, electrochemically 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.²⁰ 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.²¹ In addition, the free fatty acids are catalyzed by phospholipase-A2 into arachadonic acid, providing the substrate for cyclo-oxygenase 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,²² 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.²³ NMDA activation is now well-established in its role of potentiating hypersensitization and neuropathic pain.²⁴

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 brain²⁵. 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 others²⁶. 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.²⁷ 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.²⁸ Recently described is the tetrapartite synapse, which includes an astrocyte, microglial cell, and pre- and post-synaptic neuronal terminal.²⁹ 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).³⁰ 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.³¹

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 interneuron³² (expression of the NK-1 receptor appears to also contribute to opioid-induced hyperalgesia and tolerance³³). 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.³⁴

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.³⁵ 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.³⁶ 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,^{37, 38} 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.³⁹ 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).⁴⁰ 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) bystander 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).⁴¹

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 cholecystikinin rather than mobilization of the hypothalamic-pituitary-adrenal axis, plays a major role in creating a chronic, hyperalgesic state.⁴²

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.

Pharmacologic Pain Management

Pain can be protective, but through the stress response it may also contribute significantly to patient morbidity and even mortality. Anxiety may contribute directly to the hyperalgesic state through cholecystikinin-mediated “nocebo” effect.⁴³ Furthermore there are no firm moments when pain turns from physiologic to acute to chronic to hyperesthetic to neuropathic. Indeed, a recent study in humans reveals that in people undergoing routine ambulatory surgery such as groin hernia repair, breast surgery, and digit amputation, acute postoperative pain is followed by persistent pain in 10-50% of patients, and chronic pain will be severe in 2-10% of these individuals.⁴⁴ Thus the priority clinicians should place upon pain management in the acute and peri-operative setting is not only to minimize discomfort in that immediate period for its own sake, but to prevent whenever possible the debilitating effects of discomfort that may result from it in the time quite distant from the original insult.

The framework of effective pain management systems rests solidly on the foundation of recognition/assessment, pre-emption, and using multiple modalities. Recognition and assessment will be covered in Session 5 of this series. Strong evidence regarding the merit of pre-emptive pain management in animals does not exist⁴⁵, and human studies are conflicting, largely due to lack of power and the confounding factor of differing methodologies.⁴⁶ However, the principle of pre-emption seems to be an important phenomenon observed in basic research, and more and higher-power trials need to be conducted to confirm its clinical impact.^{47, 48} 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.^{49, 50, 51, 52, 53}

Chronic pain is not merely acute pain of extended duration. Rather, it is a maladaptive state whereby the discomfort transcends the original injury or stimulus, and becomes instead an innate feature of the central nervous system. Normal nociception is replaced by a constellation of microanatomic, physiologic, and molecular changes both centrally and peripherally, which result in an increased sensitivity to both noxious and non-noxious stimuli. Details of those changes have been described above.

The process of hypersensitization is fluid one, with variables such as intensity of stimulus, duration of stimulus, and biologic variation among patients. The clinician should be aware that “chronic pain” does not equate in veterinary patients strictly to “osteoarthritis” which provides the classic model. Indeed, the experience in humans is that after “routine” ambulatory surgical procedures, 10-50% of patients continue to encounter chronic pain, and in 2-10% the pain is severe.⁵⁴ A different study revealed that 62.7% of patients reported pain related to their injury at 12 months – 1 – year! - post-trauma.⁵⁵ Thus a first step in dealing with chronic pain is to attempt to mitigate it with the use of aggressive acute (particularly peri-operative and post-trauma) pain management.

What patients actually experience in the chronic pain state is hyperesthesia (whereby pain is perceived disproportionate to the stimulus) and allodynia (whereby innocuous stimuli are perceived as painful). How it affects them is where our clinical acuity is overshadowed by our personal biases and the many subtle adaptive abilities of our non-verbal patients. In fact it is suggested that the term “chronic pain” is better replaced by the behaviors it elicits, what we and the pet owners would understand as *disabilities*. If pets are no longer able to do the things they once did, as well or as often as they once did, then it is fair to call that a disability; and it then becomes that much easier for the owner and the clinician to observe that they are improving mobility, abilities, interaction with the pet owners, and other improvements in quality of life, than it is to see “pain relief”...when in reality they are doing all of these things. In humans these disabilities are not only the obvious limitations of ambulation and movement that we tend to scrutinize in pets, but include an entire spectrum of psycho-social and mental impairments (memory, learning, attention deficits)⁵⁶, and we have little reason to doubt that animals experience some if not all of these consequences as well. Indeed, not to aggressively recognize and address disabilities allows undermanaged pain to become a criteria for euthanasia.

Interventions may be both pharmacologic and non-pharmacologic in nature, and are complementary rather than exclusive of one another (the latter will be discussed in Session 4 of this series). A sophisticated, integrative system for pain management in primary care will include the use of many such interventions, few or any of which are not within easy (and usually cost-effective) reach of the primary care clinician. Additionally, the clinician should not be limited to considering acute pain as only resulting from surgery or trauma. Many medical conditions can be profoundly painful, including but not limited to acute pancreatitis, severe gastroenteritis, urinary obstruction, and many other conditions.

There are several pharmacologic classes of drugs which may be employed in the acute and post-operative care setting. A brief discussion of each follows:

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,⁵⁷ 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,

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;⁵⁸ 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 PGE2.⁵⁹ Lipoxygenase 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 increases the chances of adverse effects, in particular GI and nephrotoxicity. 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 NSAIDs), or were given higher than recommended doses for extended periods of time.⁶⁰ To wit, the American Gastroenterological Association reports that 44% of respondents in a survey reported personally using higher than the recommended doses of NSAID,⁶¹ 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 $24 \times 3 =$ every 72 hours or once every 3 days).⁶² 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 NSAIDs.⁶³ 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.⁶⁴ Where possible, the use of other modalities may allow lower NSAID doses which may in turn increase the safety profile. 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 $\frac{3}{4}$ 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.⁶⁵

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.⁶⁶ 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.⁶⁷

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

potassium influx. The resulting effect is hyperpolarization of the neuron and blockade of Substance P release. Nociceptive transmission is thus greatly impeded.⁶⁸

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 center⁶⁹). Cats lack glucuronate metabolism, resulting in minimal production of the analgesic M6G metabolite⁷⁰, therefore morphine may not be the ideal opioid for use in this species. Oxymorphone (Numorphan) and hydromorphone (Dilaudid) 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.⁷¹ Fentanyl in a transdermal patch (Duragesic) 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.^{72, 73} 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 species⁷⁴, with kinetics nearly identical to IV and IM administration,⁷⁵ and eliciting very little sedation. 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) is another non-scheduled (for now) opioid with 1/100th of the affinity for the mu receptor as morphine but a much better analgesic effect than this would predict. This is likely due to the combined effect of a highly active M1 metabolite and serotonin (an inhibitory neurotransmitter) agonism. Recent work demonstrates that it appears to have a very short half-life (1.7 hours) in the dog,⁷⁶ so for full effectiveness it may need to be given as often as every 6 hours, which may or may not be an obstacle for short-term administration. However, tramadol has also become a popular adjunct to chronic pain management in both human^{77, 78} and veterinary medicine, though its dosing interval long-term is not likely to be sustained at maximum frequency. One unpublished study on the effectiveness of tramadol administered once daily in canine osteoarthritis appears encouraging.⁷⁹ The incidence of dependence in humans may be substantially higher than previously suspected,⁸⁰ meaning that the drug may move to a controlled status (in some states it already has). Tramadol should not be used with other serotonergic medications such as tricyclic antidepressants.

Nalbuphine is an injectible mu-antagonist, kappa agonist similar to butorphanol but at a lower cost and is currently not a scheduled drug. One recent study in humans reports success with repeated weekly injections in relieving patients previously suffering from refractory chronic pain.⁸¹ Methadone may be an increasingly attractive alternative for mild- to moderate pain due to its safety profile and efficacy^{82, 83}, due in part to its possible additional action as an NMDA antagonist, but must be handled administered and monitored carefully owing to the fact that its sedative properties extend past its analgesic effect, which can (and in humans, does) lead to catastrophic overdose; the author has limited experience utilizing these promising modalities.

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.⁸⁴ In the chronic setting, opioid tolerance is a common sequela. As effectiveness diminishes and dose requirements escalate, undesirable adverse effects become more likely (most commonly reported in humans by far is constipation; but abnormal pain sensitivity, hormonal changes, and immune modulation are also reported though their mechanisms are not fully established⁸⁵), and the practitioner must also always be vigilant regarding drug diversion. Historically, opioid use in chronic pain has been most commonly reserved for palliative care and breakthrough pain (BTP), often of cancer patients. However, as opioid interaction with a variety of non-opioid receptors (e.g. NMDA, alpha2 adrenergic) has become more evident, the role of opioids is being redefined for their utility in a multi-modal approach to chronic pain conditions,⁸⁶ including osteoarthritis.⁸⁷ Furthermore, novel Peripherally Acting Mu Opioid Receptor Antagonists (PAMOR) are in

the final stages of development; taken with an oral opioid, PAMORs will permit the central analgesic effect of the opioid but block their effect on gastrointestinal motility. Such medications hold great promise in minimizing constipation, which commonly forces the withholding of opioids.⁸⁸ Hydrocodone, codeine (alone and in combination with acetaminophen), and sustained-released forms of oral opioids include morphine (MSContin), oxycodone (Oxycontin), and oxymorphone (Opana ER)⁸⁹ are all available by prescription, as well as transmucosal preparations such as fentanyl buccal tablets (Actiq, Fentora), though pharmacokinetics and pharmacodynamics in dogs and cats is less established. Rectal suppository opioid formulations may also be prescribed, but appear to provide little advantage in bioavailability over the oral route in the dog.⁹⁰ Dextromethorphan, a non-controlled weak opioid has a reported NMDA antagonism action, but it appears that the dog does not make the metabolite necessary to achieve this effect.⁹¹

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

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,⁹² including in the dog.⁹³

Local Anesthetics

Local anesthetics were once a mainstay of pain management in veterinary medicine, and may now be one of the most under-utilized modalities. They exert their action by binding to a hydrophilic site within sodium channels, thereby blocking it and disallowing the Na⁺ influx; thus neurons may not depolarize and thus the effect can be complete anesthesia to a site rather than mere analgesia. Various local anesthetics will have variable onsets and duration of action, and they may be combined for a rapid and extended effect. 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 blocks⁹⁴, 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.⁹⁵ Commercial transdermal products (EMLA, or the generic lidocaine/prilocaine formulation) are extremely useful in facilitating catheter placement and for minor procedures involving the dermis and epidermis, and 5% lidocaine patches (Lidoderm) provides post-operative wound paraincisional analgesia.⁹⁶ However, Lidoderm patches in fact are manufactured and labeled for post-herpetic neuralgia (Shingles), a very common form of chronic neuropathic pain in humans. One recent study of humans with moderate-severe stifle arthritis did report significant reduction in pain intensity after 2-week use of Lidoderm patches.⁹⁷ Their potential for use in animals for chronic pain conditions remains plausible but no applications are described in the veterinary literature. Loco-Regional bupivacaine blocks applied in humans (using Nerve Locator devices) can have hypoalgesic effects long surpassing the expected duration of action of the drug, through uncertain mechanisms.⁹⁸ Lidocaine administered intravenously has been shown in humans to speed the return of bowel function, decreases

postoperative pain, minimize opioid consumption, and shorten the hospital stay after abdominal surgery;^{99, 100} Systemic, intravenous infusion of lidocaine has also been shown to elicit a sustained effect on neuropathic pain in humans,¹⁰¹ and may have a specific point of action in the brain.¹⁰²

Capsaicin is a pungent ingredient derived from hot peppers. It has a high affinity for the TRPV1 receptor on peripheral A-gamma and C-fiber nerve endings, and once bound elicits both rapid and long-acting hypoalgesia at the site due to reversible as well as non-reversible ultra-structural changes. A rat model has demonstrated the effectiveness of locally-applied capsaicin at reducing post-operative hypersensitivity,¹⁰³ and this compound has also been used in humans for chronic peripheral neuropathies and musculoskeletal pain.¹⁰⁴

Note: Formulas for a combination morphine, lidocaine, and ketamine constant rate IV infusion has been described in dogs.¹⁰⁵ The combination is profoundly analgesic, fairly sedating, and is superior for the most painful post-operative states. 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.

Gabapentin

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.¹⁰⁶ In a study of women undergoing hysterectomy, only the patients receiving both NSAID and gabapentin were completely satisfied with their post-operative pain management, when compared to women receiving either NSAID or gabapentin alone,¹⁰⁷ and in a meta-analysis of 896 patients undergoing a variety of surgical procedures, gabapentin significantly reduced pain at both 4 and 24 hours post-op when compared to placebo.¹⁰⁸ Pharmacokinetic studies in dogs reveal that it may have a half-life of 3-4 hours in the dog¹⁰⁹, suggesting a TID administration schedule. The primary adverse effect in dogs appears to be somnolence (as in humans) which usually will spontaneously resolve over a few days acclimation time.

Gabapentin has become a popular in human medicine since its introduction in 1994 for many chronic and neuropathic pain conditions.^{110, 111, 112, 113, 114} However, a TID administration schedule may be difficult to sustain long-term, and no veterinary studies are currently published on its use. However, anecdotally, BID administration does appear to achieve a clinical effect in dogs. Interestingly, in a rat model there is recent evidence a gabapentin-like analog has reduced the development of experimental osteoarthritis.¹¹⁵ The adverse effect of somnolence can be mitigated by starting off at quite low doses and tapering upwards. Pregabalin (Lyrica) is new generation compound, labeled for use in diabetic neuropathy and post-herpetic neuralgia; its utility in animals remains unknown at this time.

Amantadine

NMDA receptor antagonism remains a research focus for chronic pain in humans,¹¹⁶ but no clinical studies report on its use for osteoarthritis. Amantadine is an anti-viral (influenza-A) compound use in humans as for treatment of Parkinson's disease due to its dopaminergic effects, and is reported to exert an analgesic effect through NMDA receptor antagonism.¹¹⁷ One study in dogs with osteoarthritis demonstrated greater improvement over 12 weeks of treatment with amantadine with meloxicam, compared to meloxicam alone.¹¹⁸ Toxicity and kinetic studies have been performed in humans,¹¹⁹ but not in dogs. Anecdotally in dogs and cats, diarrhea is commonly noted and agitation less frequently.

Tricyclic antidepressants:

TCA's exert their analgesic activity by blocking norepinephrine and serotonin (5-HT) reuptake in the dorsal horn synaptic cleft of inhibitory neurons that have descended from the medulla oblongata and mesencephalon; this allows these inhibitory neurotransmitters to exert a prolonged and more pronounced effect. Since depression (pain-related and otherwise) is also mediated through NE and serotonin, patients may have benefit of TCA's from these co-existing but distinct mechanisms. Other additional effects include interaction with NMDA activity and sodium channel blockade. As a class, TCA's are a first-line medication for neuropathic pain in humans,¹²⁰ and amitriptyline is the most commonly used TCA in both humans (primarily for diabetic neuropathy)¹²¹ and animals (primarily for chronic feline interstitial

cystitis¹²²). It has a balanced NE and serotonin effect, and thus is among the more sedating, anti-cholinergic, and effective of various TCA's.¹²³ Newer TCA's such as duloxetine (Cymbalta) developed for diabetic neuropathy have more strict serotonin (i.e. NE-sparing) activity, diminishing their adverse effects; its clinical use in animals has not been documented. TCA's should not be used with other serotonergic medications such as tramadol.

DMOAA

Disease-modifying osteoarthritic agents are products that are not FDA-approved medications or are not known to have a primary analgesic mechanism of action, or both, but which seem to have a positive influence on patients with osteoarthritis. The polysulfated glycosaminoglycans exert their action by inhibiting collagenase and promoting the formation of fibrocartilage, which should have the dual effect of improving the clinical status of the patient as well as slowing the course of osteoarthritis. While not entirely a settled matter in humans, evidence is beginning to accumulate that the combination of glucosamine and chondroitin (not either one used alone) exerts a positive structure-modifying effect on the cartilage, thus interfering with the progression of OA.¹²⁴ The only FDA-approved drug in this category is Adequan, which in the author's hands has a more rapidly demonstrable and reproducible effect¹²⁵ than oral supplements. Adequan may be administered (off-label) via a subcutaneous route with similar bio-availability as the IM route, allowing it to be dispensed for the owner to give at home. This decreases considerably the cost and inconvenience to the owner, which in turn adds greatly to compliance. The author also uses it regularly (off-label, currently) in cats.

Disease-modifying osteoarthritis agents may play a role in diminishing post-arthroscopy pain. One recent study demonstrated that post-operative intra-articular injections of hyaluronan diminished afferent nociceptor activity up to 1 week in a guinea pig model of experimental anterior cruciate ligament transection and partial meniscectomy.¹²⁶

Systematic reviews of neuropathic pain in humans recommend a treatment algorithm, regardless of etiology, that includes drugs of first choice tricyclic anti-depressants, gabapentin, and opioids. However, these papers are drawn mainly from trials involving diabetic neuropathy and post-herpetic neuralgia, conditions yet to be documented in animals, and effectiveness of these medications has not been demonstrated for the most common neuropathic pain condition in humans, lumbar radicular pain (sciatica).¹²⁷

Non-Pharmacologic Pain Management

No discussion of acute and chronic pain management is complete without strongly advocating the use of tools and techniques known to enhance comfort and recovery, outside the western-oriented construct of drugs and medications. In the acute setting, this may include ensuring that recovery cages are padded, footing is secure, cold-packs applied to surgical sites, supportive bandages applied where possible, and so on; also synthetic feline facial pheromone has been shown to calm cats and may diminish the sympathetic contribution to pain pathways.¹²⁸ In the chronic setting, environmental modification at home to enhance the pet's ability to navigate its surroundings (ramps, throw-rugs on slick floors, etc.) seem intuitive but should not be omitted from clearly stated recommendations to clients.

For post-operative patients, surgical technique may be a contributing factor in pain management. In cats undergoing onychectomy, a recent study using pressure platform gait analysis reported that the use of CO2 laser allowed more rapid return to function than a scalpel/tourniquet/bandage technique.¹²⁹ Minimally invasive surgical techniques (e.g. laparoscopy, thoracoscopy, arthroscopy) causes much less tissue damage – therefore less inflammation, therefore less pain, therefore faster recovery – than traditionally invasive surgical approaches.¹³⁰ Interestingly, one recent study that examined experienced vs. inexperienced surgeons found no difference in post-operative pain-related behaviors, belying the argument that faster surgeons with smaller incision lines need be less concerned with post-operative pain management.¹³¹

Weight Management

Weight loss may be among the most meaningful interventions in patients with chronic pain. Indeed, one study in dogs reports substantial improvement in lameness associated with osteoarthritis from weight loss alone.¹³² Not only does a lean body score reduce mechanical load-bearing on joints, adipose tissue is being increasingly recognized as the body's largest endocrine organ, secreting a variety of familiar and also newly-discovered hormones and pro-inflammatory cytokines ("adipokines")¹³³ that can contribute directly to various systemic disease states, including the progression of osteoarthritis.^{134, 135} It has previously been demonstrated that prolonged diet restriction (and maintaining a lean BCS) can diminish the severity of OA.^{136, 137}

Dirlotapide (Slentrol®) is a selective inhibitor of intestinal MTP (microsomal triglyceride transfer protein), which in turn stimulates the production of peptide YY, which in turn binds to the satiety center of the hypothalamus and can reduce dietary food intake by 40% with attendant weight loss.^{138, 139} The author has found dirlotapide quite effective particularly in patients classified as morbidly obese and refractory to other weight reduction programs. Potential adverse effects appear to be uncommon but include vomiting, diarrhea, and steatorrhea.

Nutritional Intervention

DMOAA

Disease-modifying osteoarthritic agents are products that are not FDA-approved medications or are not known to have a primary analgesic mechanism of action, or both, but which seem to have a positive influence on patients with osteoarthritis. The polysulfated glycosaminoglycans exert their action by inhibiting collagenase and promoting the formation of fibrocartilage, which should have the dual effect of improving the clinical status of the patient as well as slowing the course of osteoarthritis. While not entirely a settled matter in humans, evidence is beginning to accumulate that the combination of glucosamine and chondroitin (not either one used alone) exerts a positive structure-modifying effect on the cartilage, thus interfering with the progression of OA.¹⁴⁰ There are several veterinary and OTC oral products available, some of which have produced studies demonstrating this effect, either alone or in combination with other compounds.¹⁴¹ Since these products are classified as nutritional supplements, they are not FDA regulated and one must remain vigilant regarding the attendant quality control issues.

Omega-3 fatty acids

Omega-3 polyunsaturated fatty acids exert their action through competitive inhibition of pro-inflammatory prostaglandin production. 33% of Americans who use complementary modalities cite pain as the reason for doing so, and omega-3 PUFA's remain one of the more well-studied modalities. Recent evidence in humans strongly suggests that omega-3 PUFA's are an attractive adjunct for treatment of inflammatory joint pain;¹⁴² similar results are being demonstrated in canine osteoarthritis.¹⁴³

Nutrition

There is growing acceptance of the important role nutrition plays in the maintenance of bone and joint health. For example, articular cartilage is critically dependent upon the regular provision of glucose, amino acids, vitamins (particularly vitamin C), and essential trace elements (zinc, magnesium, and copper), and imbalances may be involved in the pathogenesis of osteoarthritis.¹⁴⁴ Commercial veterinary diets have been formulated with joint health specifically in mind (e.g. Hill's J/D¹⁴⁵, Purina JM, Eukanuba Senior Plus) and the author makes routine use of this modality. While different formulations, a common feature to them is substantial supplementation with omega-3 fatty acids.

Microlactin

This oral byproduct of the milk from hyper-immunized cows exerts its action by unknown mechanisms, but there is evidence of its suitability for use in patients with chronic osteoarthritis.¹⁴⁶

Physical Rehabilitation/Physiotherapy

In particular for orthopedic surgery, it is a settled matter that a physical rehabilitation program will speed return to function.¹⁴⁷ Optimally, PR programs are most effectively accomplished in referral practices

with certified individuals and extensive equipment, most notably the underwater treadmill. In the absence of that availability, it is the author's view that basic and rudimentary techniques can be learned and applied in the primary care setting, while also teaching the owner how to have their pet perform specific exercises at home. Transcutaneous and percutaneous electrical nerve stimulation (ENS) is a validated technique in humans¹⁴⁸, and a recent study in dogs demonstrated that a dietetic program accompanied by referral for intensive physiotherapy provided for improved weight loss and limb function (measured by force plate analysis) when compared to an at-home program (though this latter set of patients also improved over baseline).¹⁴⁹ Massage has been demonstrated to improved pain and disability scores in humans with stifle osteoarthritis.¹⁵⁰ Providing environmental enrichment and promoting simple activity may minimize chronic discomfort, as human studies have shown that patients who avoid activity suffer the greatest physical disability and distress.¹⁵¹

Photobiomodulation

It has long been demonstrated that certain wavelengths of light interacting with tissue can stimulate ATP production, DNA synthesis, cell membrane permeability, and the production of nitrous oxide (which inhibits neutrophil adherence to vascular endothelium). The clinical affects appear to be anti-inflammatory, analgesic, and improved microcirculation. The value of laser to deliver light into joints for therapeutic effect is under increasing investigation with encouraging results.^{152, 153} At least one unit has FDA approval for this utility (www.klaserusa.com), and the author routinely uses this modality with a variety of acute and chronic painful conditions.

Acupuncture

The National Institute of Health published a consensus statement acknowledging efficacy of acupuncture in dental pain, and supporting it as an adjunct treatment in a wide variety of other painful conditions.¹⁵⁴ The role of placebo effect in acupuncture is difficult to determine in humans, much less animals. One recent set of studies illuminated that patient expectations of acupuncture positively correlated with treatment outcomes.¹⁵⁵ However, similar effects can be expected with most any non-blinded treatment modality, and in the author's experience with very basic acupuncture techniques, approx. 2/3 of clients attribute enough of a positive effect to the acupuncture to continue it on an intermediate- to extended course.

Veterinarians have an astoshingly wide and diverse pain management arsenal from which to draw, virtually none of which is beyond the reach and utility of the primary care clinician. The author recommends a "Rule of 3, or 4 or More", that is, each patient identified with a painful condition or potentially painful condition should receive at a minimum of 3 interventions, and possibly more. These interventions might utilize pharmacologic or non-pharmacologic techniques. The presence of pain elicits a constellation of variable – and likely patient-specific – changes in gene, neurotransmitter, and receptor expression, what is called the "neurobiological signature" of a particular condition. Future efforts will focus on the development of interventions that target the particular signature, and ultimately, for a particular patient.

Veterinarians with a special interest in the field are encouraged to join the International Veterinary Academy of Pain Management (IVAPM): www.ivapm.org. In addition to the resources and value of membership, IVAPM also provides a track to earn the designation of Certified Veterinary Pain Practitioner (CVPP).

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