

Opioid-Sparing Pain Therapy in Animals: Working Task Force

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Purpose: The purpose of this consensus report is to address issues associated with the availability of opiate therapeutics in veterinary medicine and to provide background information, guidance and recommendations so that veterinarians can reduce the use of opioids in animals by implementing a comprehensive, patient-centered, multimodal and multidisciplinary approach for the treatment of acute pain in companion animals.

INDRODUCTION

Opioids are among the most effective analgesics. Their use in the management of acute pain in dogs, cats and horses, either alone or in combination with other analgesics, is well documented and accepted. (Ref) Derived from the opium poppy, the analgesic effects of opioid analgesics primarily reflect their interaction with mu and kappa opioid receptors in the neuroaxis which are coupled through G proteins to regulate nociceptive processing.¹ Full mu agonists (e.g., morphine, hydromorphone, and fentanyl) typically display the strongest analgesia, but correspondingly present the greatest risk of adverse receptor-mediated drug effect including euphoria, dysphoria, urinary retention, ileus, post-operative nausea/vomiting (PONV) and/or inappetence, and most recently a paradoxical enhancement of nociceptive processing (e.g. opioid-induced neurotoxicity resulting in hyperexcitability and hyperalgesia) especially in herding dogs.²⁻⁴ In contrast, partial mu agonists (e.g. buprenorphine) and agonists that activate kappa receptors (e.g., butorphanol) display more restricted efficacy in severe pain states, are considered to be less effective as analgesics, but are also associated with fewer dose limiting adverse drug effects (ADEs).⁵ As with many drugs that act through G protein coupled receptors opioids are associated with the development of tolerance (e.g. the need for a higher dose to bring about a given pharmacologic effect) and physical dependence (habituation).⁶ Rapid discontinuation after prolonged use may lead to clinical signs of withdrawal.⁷ These latter phenomena are generally of less concern in animals because opioid use is generally limited to short-term management of acute pain.

The euphoric effect of mu agonists, dependency, and the adverse condition of withdrawal in humans has led to the current epidemic of opioid abuse ("opioid crisis" in humans).⁸ According

to the National Institutes of Drug Abuse, the opioid epidemic began in the late 1990s largely as a result of the perception that pain patients should not be denied opiates and that patients in pain would not suffer addiction liabilities. This perception in both the research and clinical practice communities was exploited by the pharmaceutical industry in the aggressive marketing of opioid based products.^a Unrestricted physician prescribing, misuse and widespread diversion has resulted in a marked and continuing increase in substance abuse, diversion (transfer of any legally prescribed controlled substance from the individual for whom it was prescribed to another person for any illicit use), and lethal overdose.⁹ This misuse has led to an opioid crisis characterized by substance abuse disorders, addiction, and a large legal, quasi-legal, and illegal market of opioid transactions, diversion and distribution, taking a monumental human and economic toll in the United States.^b

The opioid epidemic is now being addressed by the US-FDA. Among other actions, Commissioner Dr. Scott Gottlieb has issued a number of statements directed toward the various prescribing medical professions, including veterinary medicine (Table 1).^c Dr. Gottlieb indicates that responsible opioid use mandates adherence to both Federal (through the Drug Enforcement Agency) and state regulations, which vary from state to state. Both must be followed when purchasing, storing, dispensing, prescribing or disposing of opioids. Decreasing diversion by human abusers depends on limiting inappropriate access while targeting more appropriate prescribing. For humans, the latter may involve increasing use of non-opioid or opioid sparing analgesic protocols, or protocols that preferentially use drugs that are not full mu agonists (such as buprenorphine) or are kappa agonists and mu antagonists (such as butorphanol) in lieu of pure mu agonists as long as patient pain can be effectively managed. Dr. Gottlieb's also acknowledges that most educational materials for the appropriate use of opioids have been directed towards human medicine, and as such, offers a "Needs to Know" education resource specifically for veterinarians (Table 1).

<https://www.fda.gov/AnimalVeterinary/ResourcesforYou/ucm616944.htm>

Among the points that Dr. Gottlieb makes in his statement to veterinarians is acknowledging that because of the limited number of animal approved opioids extra-label drug use of human opioids in animals is significant. He emphasizes that Extra-Label Drug Use (ELDU) must adhere to the regulations as defined in the Animal Medicinal Drug Use Clarification Act (AMDUC) of 1994 and refers to their delineation by the American Veterinary Medical Association (Table 1).^d The requirements for EDLU in non-food animal includes the lack of an animal approved drug that will meet the needs of the patient. However, the Act also addresses use of compounded products, for which the requirements are more restrictive: compounded products are allowed only if neither a human nor animal approved drug is available to meet the patient's needs. For example: while drug shortages are a justifiable reason for using a compounded opioid, cost is not (Table 1).

The opioid epidemic is having profound a collateral effect on opioid availability and use by the veterinary profession. As distributors are increasingly faced with fewer products from manufacturers, they may also decide to no longer carry, restrict, or in the extreme simply will not make available human opioid products for veterinary distribution. For example, morphine, hydromorphone and fentanyl injectables are cited by the FDA as drugs for which there is a shortage. Veterinarians have had some distributors either not be able to or decline to distribute

these drugs. Inquiries can be made to the Center for Drug Evaluation and Research (CDER, human side of the FDA) about the drug shortages.^e

Although neither the FDA nor the DEA suggest any intention to directly limit the availability of opioid drugs for veterinary use, the marketplace has done so. Veterinarians (and researchers) are experiencing an interrupted and restricted availability of full mu agonists in common clinical use including morphine, hydromorphone, and fentanyl.^f

This restricted availability is due to a convergence of factors:

- As human medicine evolves in the direction of opioid-sparing strategies, the demand and hence supply of full-mu agonist opioids diminishes. What product is available will always funnel first to human medicine, with remaining supplies allowed into the pipeline for animal use.
- The federal government has directed decreasing production of certain highly abused schedule II opioids
- Hurricane Maria damaged and closed large number production facilities in Puerto Rico, which are not back online.
- Pfizer does not anticipate that it will resume sales of injectable opioids to the veterinary market until mid-2019.^g

The chronic administration of oral opioids in veterinary medicine is not recommended since most have poor bioavailability in animals or produce undesirable side effects. At the present time, a shortage of opioids labeled for veterinary use in the United States does not appear to be at hand. Therefore there is no expectation of restricted availability of Simbadol®, Buprenorphine-SR®, Torbugesic®, and Torbugesic-SA® for the foreseeable future. This could change if marketplace or other conditions begin to limit the availability of Active Pharmacologic Ingredients (API; i.e. the raw material's) used in manufacturing of opioid products.

PAIN MANAGEMENT AND REDUCING OPIOID USE IN VETERINARY PRACTICE

As the availability of full-mu agonists becomes increasingly unpredictable and limited, the imperative for development of non-opioid (or opioid-sparing) analgesic strategies and protocols increases. This may become even more paramount if animal pharmaceutical companies implement decisions that decrease the availability of animal-approved opioids. Such policy decisions could include limiting injectable opioids to preservative-free, single-use formulations (i.e. discontinuing multi-dose vials), substantially increasing costs to veterinarians. The Center for Drug Evaluation and Research (CDER), which approves human drugs, already weighs in on animal opioids as is demonstrated by warnings on animal drug package inserts that address potential human exposure, whether accidental or intentional. However, this increased awareness of FDA concerns regarding human access to veterinary drugs may act as a deterrent to a company to pursue an animal label for a scheduled opioid substance. The human opioid epidemic has emphasized the need for the veterinary profession to actively pursue approaches that will minimize opioid use and its availability for diversion and abuse. Increasing attention on the human opioid epidemic and the need for the veterinary profession to assume, if not actively pursue, an approach that will help to minimize the “opioid crisis”, by swiftly adapting to

the acute and likely persistent shortage of full mu agonist opioids will add in addressing the problem. This White Paper focuses on opioid use for acute and peri-operative pain.¹⁰

PAIN MECHANISMS

The acute injury pain phenotype: Acute pain refers to pain that is generated in response to tissue injury; to be distinguished from the transient physiologic sensation which occurs in response to a harmful insult that does not lead to tissue injury (e.g., touching a hot stove but removing your hand before it is burned).

The pain sensory phenotype, is initiated with the onset of injury and typically persists through the course of healing.¹¹⁻¹³ The time course of wound healing has been extensively reviewed.¹⁴⁻¹⁶ Typically there are three phases; i) The acute phase: wounding is characterized by clinical signs of inflammation (heat/warmth erythema, pain, and swelling) lasting approximately 72 hrs. ; ii) Subacute (Proliferative/Reparative): reflecting resolution of inflammatory signs accompanied by angiogenesis, fibroplasia, increased collagen production and epithelization.¹⁶ This phase typically lasts 1-3 weeks, depending on tissue type. Surgical wounds are still at risk of re-injury and trauma or excessive motion at the surgical site can lead to delayed healing and prolonged inflammation and pain; and, iii) Chronic (Maturation/ Remodeling): representing remodeling of collagen and connective tissue and contraction of the surgical scar, with this phase lasting weeks to months.

The initial inflammatory phase of tissue injury is characterized by an ongoing aversive pain originating at the site of tissue injury that is typically associated with an exaggerated response (1^o hyperalgesia) to secondary to a mild stimulus applied to the injury site. Non-injured tissue immediately adjacent to the injury site may also be painful (2nd hyperalgesia or allodynia).¹⁷ The mechanisms common to such tissue injury are applicable to virtually every exterior (skin, corneal, oral mucosa) and interior (hollow visceral organs, meninges, muscle, joint and bone). On a cellular level, this phase includes migration of platelets, erythrocytes and leukocytes to the site(s) of injury with release of degradative proteases, inflammatory proteins, and immunomodulatory cytokines. These factors act on terminal receptors of A δ (small myelinated) and C poly modal (unmyelinated) nociceptors evoking kinase mediated phosphorylation yielding increased terminal excitability leading to ongoing terminal activity and sensitization of the terminal accounting for the development of primary hyperalgesia.¹⁸ C fiber afferent traffic leads to increased dorsal horn excitability (wind up in the second order projection neurons). Astrocytes and microglia release excitatory products and descending pathways from the brainstem terminate in the dorsal horn excite dorsal horn neurons.¹⁹ The collateral projections of afferents and intersegmental projections of the second order neurons lead to an increased receptive field of the segmental neurons and account for the emergence of the 2nd hyperpathia. The net effect is to increase afferent evoked dorsal horn outflow to the brain. These projections to the brain terminate in the somatosensory cortex and limbic forebrain (anterior cingulate), mediating the sensory-discriminative and affective-motivational (distress; suffering) aspects of pain processing.²⁰⁻²³

Chronic pain mechanisms secondary to tissue injury: Continued low-grade or intermittent inflammation and pain can contribute to chronic, non-healing wounds and chronic pain states.^{24,25} Pain may not resolve in a significant fraction of human surgical patients leading to the notion of an “acute to chronic pain transition” or “pain chronification” (Persistent postsurgical pain: PPSP).²⁶⁻²⁸ A similar transition is believed to occur in animals. Pain chronification (the process of transient pain progressing into persistent pain), and coincident chronically painful conditions (ex. osteoarthritis) suggest that perioperative pain management requires treatment beyond what may be expected for the individual procedure.

Mechanistically, pain chronification likely arises from injury to nerve trunks resulting in abnormal and unpleasant sensation (i.e. dysesthesia) and sensitivity to otherwise non aversive stimuli (allodynia). This pain is referred to the distribution of the injured nerves and often fails to resolve due to irreversible changes to nerve function.²⁹ The nerve injury leads to ectopic activity at the injury site and the dorsal root ganglion cell of the injured axon.³⁰ These effects upon dorsal root ganglia (DRG) function resemble a neuroinflammatory reaction that leads to significant changes in gene expression, altered expression of pro-excitatory receptors and channels, and the invasion of macrophages in the DRG.³¹ Alternatively, there is appreciation that a chronic pain state leads to a condition which converges on having a neuropathic pain phenotype. For example, bone or joint injury or chronic inflammation of the joint (ex. osteoarthritis) can lead to hyperinnervation of joint and soft tissue by small afferents with terminals which have a neuroma phenotype.^{24, 32} Chronic pain states arising from frank nerve injury and persistent inflammation have comparable mechanistic components: peripheral transduction occurring at the normal nerve ending or at a specialization that arises at the injury site of the nerve (neuroma); activation of a primary afferents; excitation of spinal systems (2nd order neurons); a complexity of spinal encoding processes that may up or down regulate the input/output function, projections to supraspinal components; and, drive elements relevant to the affective content of the stimulus. Importantly, approaches to the most effects methods for providing adequate analgesic therapy in order to prevent or reduce this transition is a subject of ongoing debate although favorable results have been observed with non opioid interventions.^{33, 34}

Note: Opioids are not recommended nor commonly used by most veterinarians to manage chronic pain states, including osteoarthritis, although their short term administration may aid in controlling acute pain flare ups in otherwise adequately treated animals. Further discussion of chronic pain is beyond the scope of this White Paper, except to say that a primary goal of managing acute and perioperative pain is to avoid persistent post-surgical pain syndrome (PPSP) and the challenges associated which chronic pain management.

STEPS VETERINARY CLINICIANS SHOULD IMMEDIATELY UNDERTAKE³⁵⁻³⁸

1. Anticipate and deploy pain-management strategies best suited for a given patient, its unique circumstances and risk factors (signalment & clinical presentation, surgical procedure, pre-existing pain/inflammatory conditions, and other co-morbidities) within the resources available to the clinician.
2. In an environment of disrupted availability of full-mu agonist opioids (e.g. morphine, hydromorphone, fentanyl), deploy opioid-sparing strategies (Table 2), to include

- a. Less opioid usage (dose, schedule/frequency/duration)
 - b. “Step down” to usage of partial mu and kappa agonist opioids, with the advisement in accordance with the FDA AMDUC’s ELDU to utilize FDA-labeled rather than compounded (a substance [i.e. drug] that is prepared in the exact strength and dosage form required by the patient) products
3. Encourage non-pharmacologic therapies, abuse-deterrent formulations (ADF’s: buprenorphine) and enhanced communication with pet owners with regards to pain, increasing their awareness and recognition of behaviors (or lack of them) related to pain, and the role that simple stress, anxiety and other elements of household environment can contribute to pain.³⁷
4. Become mindful of signs suggesting opioid diversion by clients, and address accordingly including, when indicated, the alerting of authorities.

ADDITIONAL STRATEGIES CURRENTLY AVAILABLE TO THE VETERINARY CLINICIAN

1. Emphasize the necessity for improved pain recognition and assessment, including the use of currently non-pharmaceutical instruments and validated clinical measurement instruments (CMI; Table 3).
2. Establish goal directed (GD) monitoring techniques for physical status, pain/pain therapy, monitor cardiorespiratory parameters that guide clinical decision-making throughout the peri-operative period
3. Establish protocols that include "Quality of Life" (QOL) and “Quality of Care” (QOC) procedures (ex. quality of anesthesia, etc.)^{39,42,43}
 - a. “Enhanced Recovery” (ASER)^{h,42, 43}
 - b. “Perioperative Quality Initiative” (POQI) consensus statement procedures.^{44,f}
4. Appreciation of the well-defined phenomenon of Persistent Post-Surgical Pain (PPSP), and the availability of strategies to mitigate and minimize the likelihood of acute pain transitioning to persistent and/or chronic pain. This includes identifying patients with risk factors for PPSP (Table 4) and modification of perioperative analgesia protocols. The development of PPSP is “recognized as a significant health problem affecting the postoperative outcome of patients, their rehabilitation, and their quality of life” (and “with important legal and medico-economic consequences”) in humans and is likely to be a similar problem in animals.
5. Develop the skills, tools, and techniques required comply with the recommendations. (Tables 2, 3).
6. Remain up-to-date on veterinary pain management practices, including regulatory, marketplace changes of both opioid and non-opioid products and tools. This may include but is not limited to: pursuing the many continuing education opportunities and maintaining a strong collaborative relationship with an American College of Anesthesia & Analgesia Diplomati (DACVAA) or a Certified Veterinary Pain Practitioner (CVPP) designation from the International Veterinary Academy of Pain Managementⁱ (IVAPM).

VETERINARY INDUSTRY STRATEGIC INITIATIVES FOR THE TREATMENT OF PAIN IN ANIMALS

1. Encourage the development of veterinary-labeled opioid therapeutics. [Promote the development of ultra short acting mu opioid agonists that carry a much lower risk of inducing opioid-induced hyperalgesia, like remifentanyl]
2. Encourage the development of non-opioid veterinary-labeled analgesic therapeutics
3. Encourage research regarding validation of pain biomarkers
4. Develop and promote veterinary education and educational portals with regards to contemporary marketplace, regulatory, and legal updates (FDA, CVM, DEA, pharma; issues of diversion, opioid production, distribution, availability, opioid-related human and veterinary guidelines etc.)

TABLE 1. Important Websites Regarding Opioid Use in Animals

The Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA); extralabel drug use:

<https://www.fda.gov/animalveterinary/guidancecomplianceenforcement/actsrulesregulations/ucm085377.htm>

FDA The Opioid Epidemic: What Veterinarians Need to Know:

<https://www.fda.gov/AnimalVeterinary/ResourcesforYou/ucm616944.htm>

FDA Center for Drug Evaluation and Research

<https://www.fda.gov/Drugs/DrugSafety/DrugShortages/default.htm>

FDA The Ins and Outs of Extra-Label Drug Use in Animals: A Resource for Veterinarians

<https://www.fda.gov/AnimalVeterinary/ResourcesforYou/ucm380135.htm>

DEA Manual for Practitioners:

<https://www.deadiversion.usdoj.gov/pubs/manuals/pract/index.html>

DEA Office of Diversion's Significant documents:

https://www.deadiversion.usdoj.gov/guide_docs/index.html

DEA Registrants that have been the focus of DEA cases since 2000.

https://www.deadiversion.usdoj.gov/crim_admin_actions/index.html

Regulations in the Code of Federal Regulations applicable to Controlled Substances.

<https://www.deadiversion.usdoj.gov/21cfr/cfr/index.html>

CVMA re: DEA Compliance issues with Veterinarians. <https://cvma.net/wp-content/uploads/2014/10/DEARegistration.pdf>

TABLE 2: Opioid-Sparing Strategies⁴²⁻⁴⁵

Many opioid-sparing drugs, modalities, tools, and techniques are currently and easily found in veterinary pain texts, monographs and peer reviewed literature. (Ref) Evidence-based data for managing acute post-operative pain will vary from the “Good” (e.g. NSAIDs, alpha-2 agonists, local/regional anesthetics) to Unresolved (Weak experimental evidence or opinion: mixed, minimal, or absent clinical evidence). It is the veterinarian’s responsibility to anticipate each patient’s prospective post-operative pain and deploy perioperative protocols (context-sensitive treatment) best suited to its needs and in alignment with the clinician’s and pet-owner’s values and resources. Pharmacologic pain therapy should focus on interventions that are not addictive, context sensitive, additive or supra-additive (synergistic) and abuse-deterrent formulations.^{37,45,46}

1. Effective:
 - a. Local anesthetics and Locoregional Blocks (epidural, caudal epidural, and nerve-location guided regional nerve blocks); consider when appropriate wound diffusion/infusion catheters, strategies to increase duration (addition of partial-mu agonist, alpha-two agonist; or use of commercial liposome-encapsulated bupivacaine)
 - b. NSAIDs (including EP4 Receptor Antagonists [grapiprant])
 - c. Alpha-2 agonists (e.g. dexmedetomidine): micro dose prn, or as constant-rate infusion)
 - d. NMDA antagonists: Sub-anesthetic/sub-dissociative ketamine constant rate infusion (CRI); Oral NDMA-Receptor antagonist e.g. amantadine
 - e. Systemic lidocaine constant rate infusion (CRI)
 - f. Gabapentinoids (e.g. gabapentin, pregabalin)
 - g. Anxiolytics pre- and post-admission (e.g. trazodone, gabapentin, midazolam acepromazine, alpha-2 agonist).
2. Unresolved:
 - a. Maropitant (*as analgesic; still advised to enhance recovery by minimizing PONV)
 - b. Acetaminophen (dogs only)
 - c. Oral tramadol (opioidergic and favorable PK in cats but not in dogs)
 - d. Cannabinoids (e.g. cannabidiol and others)
 - e. Others multifunctional therapies: Tricyclic antidepressants (e.g. amitriptyline); serotonergic, noradrenergic reuptake inhibitors (SNRI’s; e.g. duloxetine, tapentadol, trazadone); monoclonal antibodies; radiosynoviothysis

Table 3. Non-Pharmaceutical Pain Therapies

1. Decrease Fear, Stress, Distress, Anxiety
 - a. Fear-Free environment & practice systems (Fear Free Certification^k; Cat Friendly Practice Program^l)

- b. Low-Stress handling (Sophia Yin's training)^m
- 2. Surgical technique
 - a. Halstead Principles (Tissue handling, etc.): The importance of surgical technique should not be underestimated as it influences tissue damage, inflammation and surgical pain. All veterinarians performing any surgery should always make every effort to employ Halsted's Principles of surgical technique: gentle tissue handling, meticulous hemostasis, preservation of blood supply, strict aseptic technique, minimize tension on tissues, accurate tissue apposition, and elimination of dead space.
 - b. Minimally invasive Surgery: Whenever technically and financially possible, minimally invasive surgical techniques should be considered. In particular, laparoscopic-assisted ovariectomy and gastropexy have been shown to cause less pain and surgical stress in small animals compared to traditional, open procedures. Likewise, arthroscopic procedures may be preferable to open arthrotomy when possible.
- 3. Use of cutting laser; evidence in veterinary medicine is limited at this time.
- 4. Cryotherapy +/- Compression: Cryotherapy includes the application of ice/ ice packs or commercial cryotherapy units directly to the surgical site. Cryotherapy leads to vasoconstriction and decreased release of inflammatory mediators such as prostaglandins, as well as slowing of nerve conduction velocity and therefore slowing or blocking transmission of pain (numbing the region). Studies have shown improvement in pain scores and decreased swelling and lameness in dogs treated with cryotherapy following orthopedic surgery. Cryotherapy using a commercial ice pack is cost effective and readily available and should be used as a routine component of post-operative pain management. The ice pack should be wrapped in a clean cloth and applied to the incision/ surgical site for 15-20 minutes. When applying to the limb, compression should be added using an Ace bandage or other elastic bandage material. Patients should not be left unattended during cryotherapy. Cryotherapy should continue until clinical signs of inflammation have resolved (heat, redness, swelling, pain on palpation)
- 5. Bladder / Nursing Care
- 6. Therapeutic Laser: The mechanism of pain relief is not fully understood, but may include: stabilization of ion channels and cell membrane resting potential, decreased nerve conduction velocity, inhibition of peripheral nociceptors, blockage of C-fiber depolarization, decreased release of inflammatory cytokines, and increased release of endogenous opioids. While there is basic science evidence to support laser therapy, there is insufficient data to confirm treatment effects in clinical veterinary patients using commercially available lasers.
- 7. Acupuncture (safe and easily applied, some basic points are thought to be pain-modifying and/or contributing to other QOL features such as anxiolysis, anti-emetic) Myofascial Trigger Point Therapy

8. PEMF: Pulsed Electromagnetic Field (Data in clinical veterinary patients is limited, but evidence from experimental studies and human patients suggests PEMF may help decrease inflammation, edema and provide pain relief).
9. TENS, NMES: Transcutaneous electrical nerve stimulation (TENS) and certain forms of neuromuscular electrical nerve stimulation may offer adjunctive analgesia in the perioperative period, but typically the analgesic effects are limited
10. Manual Therapies: (e.g. massage, passive range of motion, stretching, and joint mobilization, performed during the post-operative period, particularly following orthopedic procedures by both trained professionals and by instructing owners to perform at home.
11. Diet / Nutrition (use of high-quality recovery diets, minimizing nausea with pre- and post-op anti-emetics e.g. maropitant; appetite stimulants e.g. carpromorelin dogs, mirtazepine cats; when necessary syringe feeding or feeding tubes)
12. Validated pain assessment instruments⁴⁷⁻⁵⁰
 - a. Glasgow Composite Measure Pain Scale
 - b. Colorado State University Acute Pain Scale
 - c. UNESP-Botucatu Multidimensional Composite Pain Scale in cats

TABLE 4. Development of Persistent Post-Surgical Pain

1. **Definition(s):** Persistent postoperative pain has been defined by the International Association for the Study of Pain as a clinical discomfort that lasts more than 2 months post surgery without other causes of pain such as chronic infection or pain from a chronic condition preceding the surgery.(Ref) According to the International Classification of Diseases persistent postoperative pain has greater intensity or different pain characteristics than preoperative pain and is a continuum of acute postoperative pain that may develop after an asymptomatic period. (Ref) International Classification of Diseases defines the duration for persistent postoperative pain at 3 months after surgery.
2. **Prevalence:** Although metrics are not available in veterinary medicine, the transition from acute to chronic pain in humans ranges from 20 - 56% (including outpatient procedures) with 2-10% experiencing persistent severe chronic pain at 6 months postoperatively. In a study looking at persistent postoperative surgical pain (PPSP) 1 year post-operatively, the degree of pain was severe in 2% of patients, moderate-to-severe in 12% of patients, and 35 – 57% had neuropathic component to their pain.²
3. **Preclinical and Post Operative Evaluation:** Of note some data has suggested that transition to a chronic pain state is dependent upon the animals pain state at the time of examination which if not considered or treated and may lead to enhanced postsurgical pain.
4. **Known Risk Factors for PPSP in humans:**
 - a. The degree of acute post-operative pain is a predictive factor for PPSP in a variety of routine surgical procedures 3–5. A study in humans (Fletcher *et al.*²) reported that every 10% increase in the time spent in severe postoperative pain was associated with a 30% increase in chronic pain 12 months after surgery.
 - b. Nerve injury (Ref)
 - c. Pre-existing chronic inflammation (Ref)
 - d. Degree of trauma (pre-existing or surgical) (Ref)

Table 5. Summary of Recommendations to Reduce Opioid Use in Veterinary Medicine

1. Incorporate and utilize validated pain assessment instruments⁴⁶⁻⁵⁰
 - a. Glasgow Composite Measure Pain Scale
 - b. Colorado State University Acute Pain Scale
 - c. UNESP-Botucatu Multidimensional Composite Pain Scale in cats
2. Incorporate “Quality of Life” (QOL) evaluative protocols and processes⁴¹
 - a. Environmental enrichment
 - b. Feline Friendly and Fear free environments
3. Establish protocols that include “Quality of Care” (QOC) procedures (ex. quality of anesthesia, etc.)⁴²
 - a. “Enhanced Recovery” (ER)
 - b. “Perioperative Quality Initiative” (POQI) consensus statement procedures^h
4. Develop and utilize “multimodal” pain therapy protocols that incorporate⁴⁵
 - a. Drug additivity
 - b. Drug supra-additivity (synergism)
5. Develop and incorporate opioid-free perioperative analgesic perianesthetic procedures³⁸
6. Supplement general anesthesia with evidence based constant rate infusion (CRI) techniques
 - a. Local anesthetics (ex. lidocaine)
 - b. NMDA antagonists (ex. ketamine)
 - c. Alpha-2 agonists (ex. dexmedetomidine)
7. Employ local anesthetic techniques including epidurals and ultrasound guided nerve blocks (UGNBs)ⁿ
8. Utilize complimentary and alternative pain therapies
 - a. physical therapy
 - b. acupuncture
 - c. others (see references)
9. Establish minimum standards and monitoring techniques for physical status, pain/pain therapy
 - a. Monitor cardiorespiratory parameters that guide clinical decision-making throughout the perioperative period
10. Establish a relationship with a pain “Expert”