The framework of effective pain management systems rests solidly on the foundation of recognition/assessment, pre-emption, and using multiple modalities. Multiple modalities allow for intervention at several different places of the nociceptive pathway, increasing effectiveness and minimizing the need for high or protracted doses of any one particular drug. It is well-established in human medicine, for example, that the use of adjunct medications will minimize the use of PCA (patient-controlled analgesia) opioids with a resultant decreased incidence of adverse effects such as nausea and constipation.$^1,2,3,4,5$

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.

TRAMADOL

Tramadol is a non-scheduled (for now) opioid (in humans) 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- and norepinephrine (inhibitory neurotransmitters) agonism. Recent work demonstrates that it appears to have a very short half-life (1.7 hours) in the dog,$^6$ and it appears that dogs produce very little of the M1 opioid metabolite.$^7$ However, tramadol has also become a popular adjunct to chronic pain management in both human$^8,9$ and veterinary medicine. Only recently have some pharmacodynamic studies demonstrated the probable clinical usefulness of tramadol in dogs,$^{10,11,12,13}$ but none so far mirror the manner in which the drug is most commonly utilized (PO trans- or post-operatively, or as an adjunct for chronic pain e.g. OA). The short half-life of the drug suggests up to a Q-6 hour treatment regime, but one unpublished abstract on the effectiveness of tramadol administered once daily in canine osteoarthritis appears encouraging.$^{14}$ The incidence of dependence in humans may be substantially higher than previously suspected.$^{15}$
meaning that the drug may move to a controlled status (in some states it already has). Tramadol should not be used – or used only very cautiously - with other serotoninergic or monoamine-enhancing medications such as tricyclic antidepressants, selegiline (deprenyl), and amtiraz.

**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. 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, 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. Pharmacokinetic studies in dogs reveal that it may have a half-life of 3-4 hours in the dog, suggesting a TID administration schedule. The primary adverse effect in dogs appears to be somnolescence (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. 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. The adverse effect of somnolescence 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.

**TRICYCLIC ANTI-DEPRESSANTS**

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, and amitryptiline is the most commonly used TCA in both humans (primarily for diabetic neuropathy) and animals (primarily for chronic feline interstitial cystitis). It has a balanced NE and serotonin effect, and thus is among the more sedating, anti-cholinergic, and effective of various TCA’s. TCA’s should not be used with other serotoninergic medications such as tramadol and SS(N)RI’s (below)

SS(N)RI’s
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.

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.

SUBANESTHETIC 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 postoperative setting., including in the dog.

Systematic reviews of neuropathic pain in humans recommend a treatment algorithm, regardless of etiology, that includes drugs of first choice tricyclic antidepressants, 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).

INTRAVENOUS LIDOCAINE

Evidence is mounting for the beneficial effects of intravenous lidocaine (IVL) on pain after soft tissue surgery in humans and and some animals. IVL markedly reduces the inhalant anesthetic requirements of patients and thus is it imperative that vaporizer settings be adjusted accordingly when IVL is used during surgery. Many types of surgical pain, as well as that of major trauma, burn and pancreatitis pain may benefit from this use. IVL can be recommended as a safe and sparing adjunct to opioid and other analgesics for surgery, trauma, and pancreatitis at a dose of 50 mcg/kg/min, in dogs; and this has been used for 24 – 48 hours. In humans it has also been shown to speed the return of bowel function, decrease postoperative pain, minimize opioid consumption, and shorten the hospital stay after abdominal surgery., Systemic, intravenous infusion of lidocaine has also been shown to elicit a sustained effect on neuropathic pain in humans, and may have a specific point of action in the brain.

Several reports of concentrations and effects of IVL in cats strongly warn that it should not be used intraoperatively in cats, because of their inability to metabolize the drug, and practitioners are advised to wait until further evidence supporting its use in non-anesthetized cats is reported.
Note: Formulas for a combination morphine, lidocaine, and ketamine constant rate IV infusion has been described in dogs. 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.

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