Pain Management in Companion Animals

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2. Describe the appropriate use, mechanism of action, and precautions for use of analgesics in the treatment of pain in dogs and cats.
3. Explain the key issues that impair the prevention of diversion in companion animal owners.

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You are working in a retail pharmacy, and one of your longtime customers brings in a prescription for tramadol for her German shepherd. As you inspect it, you cannot believe the prescription is real. It reads: give 250mg every 6 hours for pain. You are perplexed as to what to do. Call the prescriber? Give the prescription back to the owner and tell her you cannot fill it? Go ahead and fill it?

The treatment of pain in companion animals (dogs and cats) involves many of the same or similar drugs as the treatment of pain in humans. Because of this, increasing numbers of animal owners are choosing to fill their pet medications in a retail pharmacy instead of their veterinarian's office. This article will provide an overview of the types of pain in companion animals, how pets manifest their pain, and how to treat it, so that pharmacists are able to provide top-of-the-line, informed care to their four-legged patients.

TYPES OF PAIN

Pain in animals is generally divided into three classifications: pathologic, neuropathic, and visceral. Visceral pain is the least understood of these, and will not be covered in this review. Pathologic pain is the most common and is the result of a noxious stimulant causing inflammation and nerve injury. Pathologic pain can be classified as acute or chronic, with the distinction between the two being a very gray area. One determination between acute and chronic pain is that acute pain cannot damage tissue, and therefore cannot cause inflammation. Most providers do not subscribe to this theory, and would prefer to define chronic pain as pain lasting beyond the expected duration of the process causing pain. Chronic pain may be associated with lasting pain from a noxious stimulus or can be autonomous in nature and have no relation to the original stimulus.

More than 200 types of chronic pain have been described, with cancer pain, osteoarthritis, and surgical pain being the most common and pertinent to veterinary medicine. In most cases of chronic pathologic pain, a heightened sensitivity of the nervous system is almost always involved, making the focus of many treatments to decrease this response. Neuropathic pain results in direct damage to the nervous system coupled with altered processing of stimuli. Manifestations of neurological pain can range from hyper-responsiveness of normal sensory input to a complete loss of sensation.

MANIFESTATIONS OF PAIN

Pain in companion animals may be difficult to recognize, as pets are not able to directly tell us when they hurt. Some symptoms of pain that is neurological in origin can include a scratching motion without touching the body, continually biting or attacking one area on the body, turning to constantly look at one area of the body, or vocalization for no apparent reason. In cats, onychectomy (declawing) can be a common source of neurological pain. Cats with this pain can show discomfort of the paws (guarding when using the paw), decreased activity and eating, and increased aggression.

Lameness, or a decrease in normal activity, is a cardinal sign of osteoarthritic pain. Additional signs include stiffness after rest, abnormal gait and a hunched appearance. With osteoarthritis, when there is constant joint pain, dogs specifically may show signs of increased nervousness, aggression, depression, and loss of appetite. Other signs of pain are generally associated with behaviors pointing to the affected organ system. For example, dermatological pain may result in sucking or chewing on the skin, while urological pain may result in difficulty voiding.

Soft tissue pain is a term that encompasses dysfunction or pain in almost all parts of the body including muscle, fascia, tendons, ligaments, cartilage, synovium, fibrous capsules, and organs. Soft tissue pain tends to be a diagnosis of exclusion as radiographic changes are not frequently present and symptoms are generally vague and only include altered behavior. The most common type of soft tissue pain in animals is myofascial pain.

NON-PHARMACOTHERAPY OPTIONS

Non-pharmacotherapy options are generally considered therapies to be used in conjunction with pharmacologic modalities. Some common non-pharmacologic therapies are described here.

Cold/Heat Therapy

As with humans, cold and heat therapy may be beneficial in dogs and cats. Cold therapy should be used for acute pain and in times where chronic pain has an acute flare. Heat therapy is beneficial in reducing pain, improving circulation, and decreasing joint stiffness. It should be avoided when swelling accompanies the pain. Hot packs can be used to heat tissues up to a depth of 2 centimeters. Both hot and cold packs should be wrapped in cloth prior to applying so as to not burn or freeze the skin, respectively. Heat lamps are also a beneficial option as most animals oppose having hot packs placed on them. Both cold and heat therapy may be used up to three times per day.

Weight Loss or Control

Weight loss or control is important in cats and dogs, especially those that suffer from osteoarthritis. In addition to putting stress on joints, obesity leads to a constant state of inflammation. Decreasing weight in companion animals can both increase mobility and decrease clinical signs of osteoarthritis. In fact, even moderate weight loss (6-8 percent) has been shown to reduce pain scores in dogs. Weight loss or control in animals generally includes a food with lower caloric content along with portion restriction.

Pet owners should consult their veterinarian for a safe and healthy weight management program.

Acupuncture and Massage Therapy

Acupuncture is a very beneficial treatment for myofascial pain. Myofascial pain occurs when there is sustained muscle contraction, resulting in a band of tightened muscles, or myofascial trigger points (MTrPs). MTrPs are not always painful at rest, but can be when palpated. However, MTrPs always result in decreased muscle strength and function. Acupuncture works by inserting a needle into an MTrP. This causes an immediate contraction of the muscle, followed by release of muscle tightness over a few seconds to minutes. The mechanism behind this release of tightness is thought to be because of increased blood flow and neurotransmitter release at the site of puncture. Acupuncture is generally well-tolerated by animals as needle placement is usually non-painful. Massage therapy is also thought to work in a similar way, as well as stretching and strengthening the muscle. Owners of animals with chronic pain often decrease the amount they touch their pet for fear of exacerbating the pain. It has been hypothesized that increased tactile stimulation, through owner touch or massage, may actually increase pain relief in these animals.

Therapeutic Exercise

Therapeutic exercise (TE) is considered by many the most important part of the healing process. TE includes passive, assisted, and active modes of therapy. In passive TE, the animal has range of motion (ROM) activities performed on it. For example, a veterinarian or therapist might place the animal on their back and work the legs in a manner that would be consistent with normal activity. ROM activities increase muscle strength, improve conditioning and endurance, and increase mobility. Assisted TE is designed to improve neuromuscular function, decrease pain, and increase strength and endurance. In assisted TE, support is placed under the affected area of the animal (usually the hind legs) in the form of a sling or in some cases, the hands of the therapist. The animal is then able to walk on its own while placing a controlled amount of stress on the affected area.

Active TE can occur in several ways. For cats especially, a good mechanism of active TE is playing with a toy such as a laser pointer or a feather on a string. Such exercise can help with both ROM and stretching. With this active TE modality, it is important to only move as fast as the cat's therapeutic progress will allow and to not injure the cat further. Aquatic therapy is another mechanism of active TE that is useful for both dogs and cats. Aquatic therapy involves an underwater treadmill that increases exercise ability by decreasing stress to painful areas of the body. Dogs generally adapt to aquatic therapy relatively quickly, but cats may need to be coaxed into this training gradually, and often with treats as a motivator. Aquatic therapy in a veterinary clinic setting is often more advantageous over lakes and pools, as the temperature can be controlled to maximize heart rate and breathing. Chlorinated swimming should be avoided as it can cause dry skin and coat, abrasive wounds at the armpit, red eyes, otitis externa, and possibly respiratory problems.

Extracorporeal Shockwave Therapy

Extracorporeal shockwave therapy (ESWT) is a therapy commonly used in humans that is just starting to catch on in the animal world. ESWT delivers high velocity sound waves either in a focused manner into deep tissues or in a broad manner to a large area of superficial tissue. Effects of ESWT have been hypothesized to induce growth factors, increase collagen synthesis, increase bone remodeling, decrease inflammatory mediators, and decrease nociceptive pathways. ESWT works best for chronic pain. Evidence for use in humans is conflicting and in dogs is weak, but this therapy may be an option, especially when pharmacotherapy use is limited. ESWT is generally administered a total of 2-3 times, approximately 2-3 weeks apart. Animals are generally sedated for the procedure as the equipment can be loud and the procedure, while not painful, can be unpleasant. Fur or hair must be clipped for maximum effect.

Therapeutic Lasers

Therapeutic laser therapy has been shown to be effective in a number of types of pain, including those that are musculoskeletal, neurological, or orthopedic in nature. Therapeutic lasers also can be beneficial in wound healing and dermatologic issues. Therapeutic laser therapy causes photostimulation deep into the cells, which results in reduced inflammation, acceleration of tissue repair, analgesia, and increased cellular metabolic activity. Therapeutic lasers range in intensity from Class 1 lasers (lowest intensity) to Class 4 lasers (highest intensity). Lasers used on animals are generally classified as Class 3 or 4.

PHARMACOTHERAPY OPTIONS

Pharmacotherapeutic options are the primary treatment for pain in companion animals. Their use in animals generally follows the outline of the World Health Organization (WHO) pain ladder.

World Health Organization Pain Ladder

The WHO has established a pain ladder for the treatment of cancer pain. It has since been applied to various types of pain, including pain experienced by companion animals. The pain ladder recommends that the treatment of pain should start with non-opioids, followed by mild opioids (such as codeine or tramadol), and then, if needed, strong opioids,

Table 1. NSAIDs Approved for Pain Management in Dogs and Cats				
Name	**Enzyme(s) inhibited**	**Dosage form(s)**	**Species**	**Dose**
Carprofen (Rimadyl®)	COX-1, COX-2	Caplets, Chewable tablets	Dog	2.2 mg/kg twice daily 4.4 mg/day once daily
Deracoxib (Deramaxx®)	COX-2	Chewable tablets	Dog	1 to 2 mg/kg once daily
Etodolac (Etogesic®)	COX-1, COX-2	Tablets	Dog	10 to 15 mg/kg once daily
Firocoxib (Previcox®)	COX-2	Chewable tablets	Dog	5 mg/kg once daily
Meloxicam (Metacam®)	COX-2	Liquid suspension	Dog	0.1 mg/kg once daily
Robenacoxib (Onsior®)	COX-2	Tablets	Cat	1 mg/kg once daily for three days

until the patient is free of pain. The WHO pain ladder also promotes the use of adjuvants in the treatment of pain. Lastly, the pain ladder promotes scheduled pain medication administration, instead of as-needed administration.

Non-Steroidal Anti-Inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are great options when it comes to treating pain that is orthopedic in nature, or post-surgical. NSAIDs work the same in animals as they do in humans: they inhibit cyclooxygenase (COX) enzymes. Two COX enzymes play a role in the modification of pain: COX-1 and COX-2. COX-1 is responsible for the production of prostaglandins (including PGE_2) and thromboxane A2, among other eicosanoids. PGE_2 is responsible for a variety of physiologic responses, including vasodilation, increased gastric mucus production, and decreased gastric acid secretion. Thromboxane A2 plays a role in platelet aggregation, as well as vasoconstriction. COX-2 enzymes also produce a variety of eicosanoids, including PGE_2 and prostacyclin (PGI_2). PGI_2 is expressed in inflamed tissues. Most notably, COX-2 enzymes are found in the dorsal horn of the spinal cord and can potentiate nociception. The use of NSAIDs for the treatment of pain in companion animals can be divided into two categories: those that are non-selective for COX enzyme inhibition and those that are selective for COX-2 enzyme inhibition. COX-2 inhibition is the primary focus of pain reduction because by inhibiting this enzyme, nociception through the spinal cord is interrupted and PGI_2 expression in inflamed tissue is decreased.

NSAIDs are associated with a multitude of adverse effects, most notably, gastrointestinal adverse events. By inhibiting prostaglandins such as PGE_2 and PGI_2, NSAIDs reduce the protective mucosal lining of the stomach. Additionally, most NSAIDs are weakly acidic, so they can directly irritate the mucosa of the gastrointestinal tract. COX-1 and COX-2 enzymes are both expressed in the canine gastrointestinal tract; therefore, inhibiting both of these can cause gastrointestinal irritation. Fortunately, it has been shown that by inhibiting only one of these enzymes, gastrointestinal irritation occurs to a lesser extent. NSAIDs can also have a negative effect on renal excretion and blood flow. PGE_2 and PGI_2 produced by COX enzymes in the kidneys are associated with inhibiting renal sodium reabsorption, therefore increasing renal sodium excretion. Additionally, PGE_2 and PGI_2 play a role in renin release, which alters the blood flow of the kidneys. By inhibiting COX enzymes in the kidney, and thereby inhibiting the effects of PGE_2 and $PEGI_2$, NSAIDs have the potential to increase sodium retention and decrease renal blood flow.

Cats appear to be more prone to the renal adverse effects of NSAIDs; therefore, these drugs are primarily used in dogs. In fact, only one NSAID has been licensed for use in cats in the United States (robenacoxib [Onsior®]). As other NSAIDs may be used off-label in cats, the International Society of Feline Medicine and American Association of Feline Practitioners offer the following recommendations for minimizing toxicity in cats: use NSAIDs with greater COX-2 selectivity, work to titrate the dose to the lowest effective dose, dose overweight cats based on lean body weight, and administer the medication with food, preferably wet food with additional water added.

NSAIDs labeled for human use frequently have too narrow of a therapeutic index in animals; therefore, their use is avoided. For example, ibuprofen was historically used in dogs prior to the availability of canine-specific NSAIDs. The therapeutic dose recommended at the time was 5 mg/kg/dose, but later, doses of 8-16 mg/kg/day for 30 days were associated with gastric ulcerations or other signs of gastrointestinal disturbances. Doses of 100-125 mg/kg/dose were associated with vomiting, diarrhea, nausea, and abdominal pain, and doses of 175-300 mg/kg/dose were associated with renal failure. Cats are also

believed to experience toxic adverse effects to ibuprofen at approximately half the dose of dogs, although no studies have been shown to test this theory. Aspirin and naproxen are equally as toxic, although aspirin may be used in very small doses for its antiplatelet effect.

A detailed list of NSAIDs approved for use in dogs and cats can be found in Table 1. When dispensing these medications, it is important to convey to the owner to take it exactly as prescribed. Owners should also be instructed to give these medications with food, and make sure plenty of water is available. As many of these medications are chewable and flavored so that dogs will easily ingest them, it is also important to instruct owners to keep this medication far out of a pet's reach.

Non-NSAID Drugs

Table 2 summarizes the drug therapy alternatives to the NSAID class.

Acetaminophen

Acetaminophen is toxic to cats, and to a lesser extent, dogs. Acetaminophen is primarily metabolized through conjugation into inactive metabolites. A minor metabolic pathway results in the formation of a highly reactive metabolite, N-acetyl-para-benzoquinoneimine (NAPQI). When the primary metabolic pathway is saturated, this minor pathway increases its metabolism of acetaminophen, thus a larger amount of NAPQI is formed. NAPQI can bind to hepatocytes, causing cellular injury and death. Additionally, NAPQI causes oxidative stress to red blood cells, causing a decreased ability to carry oxygen, resulting in methemoglobinemia. In cats, an acetaminophen dose of 10 mg/kg can be toxic, therefore its use must be avoided. Acetaminophen can be safely used in dogs at a dose of 10 mg/kg twice daily, with toxicity seen at doses above 100 mg/kg. As such, acetaminophen is rarely used alone in dogs, but is occasionally used in combination with medications such as codeine or hydrocodone.

Tramadol

Tramadol [Ultram®] is a synthetic analogue of codeine and is approved to treat moderate to moderately severe pain in humans. Tramadol is metabolized into over 30 metabolites, but only tramadol itself, and two metabolites, O-desmethyltramadol (ODM) and N, O-didesmethyltramadol (DDM) have been shown to produce analgesia. Tramadol exerts an analgesic effect by agonizing mu opioid, alpha-2, serotonin 4-hydroxytryptamine [HT]-2, and muscarinic M1 receptors. It has been hypothesized that the ODM metabolite works primarily on the mu opioid receptors, with DDM secondarily affecting this receptor. Dogs have been shown to metabolize tramadol into DDM effectively, but ODM quite poorly. Therefore, it stands to reason that tramadol does not exert a substantial analgesic effect in dogs. This, coupled with the rapid half-life of tramadol in dogs of approximately 1.1 hours (as compared to 5.6 hours in humans), means that tramadol doses, and even frequencies, are much higher in dogs as compared to humans. The recommended starting dose of tramadol in dogs is 5 mg/kg every 6-8 hours. This may be increased to 10 mg/kg in dogs that are unresponsive to lower doses. Cats, on the other hand, metabolize tramadol readily into the ODM metabolite. They also eliminate tramadol at a slower rate, with a half-life of 4.5 hours. The recommended starting dose in cats is 1-2 mg/kg twice daily.

Table 2. Non-NSAID Pharmacological Therapies and Adjuvants for the Treatment of Pain in Animals

Drug	Species	Dose
Acetaminophen	Dogs	10 mg/kg twice daily
Tramadol	Dogs, Cats	5 to 10 mg/kg every 6 to 8 hours (dogs) 1 to 2 mg/kg twice daily (cats)
Codeine	Dogs, Cats	0.5 to 2 mg.kg every 6 to 12 hours
Buprenorphine	Cats	0.01mg to 0.03 mg/kg every 8 hours
Hydrocodone	Dogs	0.5 mg/kg every 12 hours
Amantadine	Dogs	3 to 5 mg/kg once or twice daily
Gabapentin	Dogs, Cats	5 to 20 mg/kg three times daily
Amitriptyline	Dogs, Cats	1 to 2 mg/kg ever 12 to 24 hours (dogs) 2.5 to 12.5 mg/cat or 0.5 to 2 mg/kg once daily (cats)

The most common adverse effects associated with the use of tramadol are nausea, anorexia, and sedation. In August 2014, the Drug Enforcement Administration (DEA) scheduled tramadol, placing it in Schedule IV. Veterinarians must be registered with the DEA and have authorization from the jurisdiction in which he/she is licensed to prescribe controlled substances. Tramadol also has a bitter taste and has been known to induce profuse salivation in both dogs and cats when ingested. Tramadol has also been known to reduce the seizure threshold in humans, and as such, should be used with caution in companion animals with a history of seizure disorders. Tramadol antagonizes the serotonin 4-hydroxytryptamine [HT]-2 receptor and therefore should not be used with other drugs that increase serotonin levels, including monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin and norepinephrine reuptake inhibitors (SNRIs). MAOIs are sometimes used in cats with Cushing's Disease, while TCAs and SSRIs are commonly used in both cats and dogs with behavior issues. TCAs also have a place in the treatment of neuropathic pain. SNRIs are rarely used in companion animals. Serotonin syndrome has been described in dogs and it presents with symptoms similar to humans including tremors, rigidity, myoclonus, seizures, hyperthermia, and salivation. Serotonin syndrome in an animal constitutes a veterinary emergency and can result in death if not treated.

Codeine

Codeine is a mu opioid receptor agonist that is approved for the treatment of mild to moderately severe pain in humans. Codeine is metabolized into several metabolites, including two predominant active metabolites: codeine-6-glucuronide and morphine. In dogs, the predominant metabolite is codeine-6-glucuronide. Pharmacokinetic studies are lacking in cats, and therefore the active metabolite of codeine in cats is unknown. The recommended doses of codeine in dogs and cats, 0.5 to 2 mg/kg every 6-12 hours titrated to effect, are anecdotal and have not been studied. Codeine is available by itself (controlled substance schedule II) and with acetaminophen (schedule III). It is important to remember when dispensing codeine that preparations with acetaminophen must be avoided in cats.

Buprenorphine

Buccal, or transmucosal, buprenorphine is an analgesic therapy primarily used in cats, but also is used in dogs. Buprenorphine is a semi-synthetic opioid that is a partial agonist at the mu opioid receptor. It binds to mu receptors, and slowly dissociates from them without exhibiting a maximum opioid effect. This causes them to have a delayed onset of action and long-acting analgesia with very few adverse effects. The transmucosal route has been shown to be a very beneficial route of administration in cats, as buprenorphine is a weak base (pKa = 8.24) and the oral cavity of the cat is slightly basic (pH = 8 to 9), leading to complete absorption. Dogs have a more acidic oral cavity, resulting in a decreased bioavailability, which limits its use in a transmucosal fashion. Transmucosal administration of buprenorphine results in a considerably greater analgesic effect than subcutaneous administration, and offers a much preferred route of administration for owners. The transmucosal dose of buprenorphine for cats is 0.01-0.03 mg/kg every eight hours. In most instances, the injectable form of buprenorphine is dispensed for oral use.

Transdermal Fentanyl

Transdermal fentanyl is a potent mu receptor agonist approved for use in humans for the management of pain in opioid-tolerant patients. Pharmacokinetic studies in dogs and cats are limited because frequently the transdermal patch is used after intravenous administration of fentanyl. It is hypothesized that dogs take approximately 24 hours to reach steady state concentrations after placement of the transdermal patch, whereas cats achieve steady state much quicker, in approximately 12 hours. Additionally, the duration of effect is relatively unknown, but is thought to be at least 72 hours in dogs and up to 104 hours in cats. The recommended dosing for fentanyl patches in cats and dogs can be found in Table 3. Patches should be placed on the dorsal or lateral thorax of the dog or cat, as placement on the limbs has not been studied. Fur or hair may need to be trimmed, and bandaging may need to be placed over the patch in order for it to adhere properly. Counsel owners not to cut fentanyl patches and not to ingest or cause any other being to ingest the patch. The Food and Drug Administration recommends that spent patches should be folded in half and flushed down the toilet to reduce the risk that a

Table 3. Recommended Fentanyl Transdermal Patch Dosing

Patient	Patch Size
Small Dogs, Cats (< 5 kg)	12.5 to 25 mcg/hr
Dogs 5 to 10 kg	25 mcg/hr
Dogs 10 to 20 kg	50 mcg/hr
Dogs 20 to 30 kg	75 mcg/hr
Dogs > 30 kg	100 mcg/hr
Amantadine	Dogs
Gabapentin	Dogs, Cats
Amitriptyline	Dogs, Cats

small child or animal pulls it out of the trash and accidentally ingests the patch.

Other Opioids

Hydrocodone is a mu opioid agonist that is used primarily as an antitussive in dogs, but can be used for pain. A dose of 0.5 mg/kg has been shown to produce plasma concentrations of hydrocodone similar to that of humans for at least eight hours. Hydrocodone is only available in extended-release or combination form, either with homatropine or acetaminophen. These combinations decrease their potential for diversion. There is little data on the use of other opioids, including morphine, oxycodone, and methadone, for the treatment of pain in companion animals. Pharmacokinetic data suggest that there is a high first pass metabolism effect of these medications in dogs, leading to low oral bioavailability and short half-lives. No studies have been published reporting the pharmacokinetic properties of oral morphine, oxycodone, and methadone in cats. Furthermore, their status as a DEA Schedule II controlled substance limits their use in animal populations.

Adjuvants

Adjuvant therapy options are generally used in addition to the primary pharmacotherapy treatments for pain. Adjuvants either help to make primary therapies work better, or can treat one facet of pain, such as nerve pain.

Amantadine

Amantadine (Symmetrel®), an antiviral commonly used in humans, has pain reduction capabilities. Amantadine is an antagonist of the N-methyl-D-aspartate (NMDA) receptor. In this capacity, amantadine can counteract central pain sensitization and decrease tolerance to analgesics. Amantadine does not work by itself but may increase the analgesic effect of other therapy options. Amantadine has only been studied in dogs, and there are no FDA licensed animal formulations. The recommended dose of amantadine in dogs is 3-5 mg/kg once or twice daily.

Gabapentin

Gabapentin (Neurontin®) is FDA-approved for use in humans for seizure disorders and post-herpetic neuralgia, but is widely used off-label for a variety of ailments. While structurally similar to gamma-aminobutyric acid (GABA), it actually does not bind to GABA receptors, but instead downgrades voltage-gated calcium channels, decreasing the release of excitatory neurotransmitters. Gabapentin should be used primarily for neuropathic pain, but has been shown to decrease pain associated with osteoarthritis, as well as post-surgical pain. The half-life of gabapentin is 3-4 hours in dogs and approximately three hours in cats, making a three times daily dosing regimen ideal. Doses of gabapentin can range from 5-20 mg/kg every eight hours in both dogs and cats. This wide dosage range is likely due to the fact that very few clinical trials have been published on its use as an analgesic. The general consensus is that it would be best used in chronic pain. Adverse effects of gabapentin in animals are similar to that of humans and can include ataxia and sedation. Commercially available formulations of gabapentin oral suspension usually contain xylitol, a potentially toxic compound to dogs. It is suggested that the amount of xylitol in this formulation is low enough so that adverse events are not seen; however caution should be exercised in dogs that receive higher doses of gabapentin, or multiple products containing xylitol. Xylitol toxicity in dogs causes hypoglycemia, which presents with very non-specific signs, including vomiting, lethargy, and weakness. It should be treated as a veterinary emergency.

An extended-release formulation of gabapentin (gabapentin encarbil [Horizant®]) has been approved for restless leg syndrome in humans. Its use has not been studied in animals, and therefore would be inappropriate to use. Pregabalin (Lyrica®), a medication that is structurally similar to gabapentin and has been approved for use in a variety of neuropathic pain conditions in humans, has been limitedly studied in dogs. Its half-life is approximately seven hours, which makes it conducive to every 12-hour dosing. However, its cost and controlled substance schedule (a DEA schedule IV) limits its use in dogs compared to gabapentin.

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) are often considered first line therapy for the treatment of neuropathic pain in humans. TCAs have a multitude of effects, including: serotonin and norepinephrine reuptake inhibition, N-methyl-D-aspartate (NMDA) receptor antagonism, voltage-gated calcium channel blockade, muscarinic receptor antagonism, nonselective histamine receptor blockade, alpha-1 receptor antagonism, enhancement of adenosine and GAB_{AB} receptors, as well as anti-inflammatory properties. Because of this assortment of effects, TCAs can produce effective analgesia, but also come with many adverse effects, including dry mouth, polyuria, polydipsia, urinary retention, blurred vision, sedation, and hypotension. Pharmacokinetic studies on the TCA amitriptyline have been completed in dogs. These studies showed that the peak plasma concentration occurred at approximately two hours, while the half-life was approximately five hours. Unfortunately, these studies did not evaluate levels of nortriptyline, the active metabolite of amitriptyline. Pharmacokinetic studies in cats were even less conclusive. The recommended dose of amitriptyline for dogs is 1-2 mg/kg every 12-24 hours, and for cats it is 2.5-12.5mg per cat, or 0.5-2 mg/kg once daily.

Glucosamine and Chondroitin

Glucosamine and chondroitin are two supplements that have been used frequently for osteoarthritis in humans. There are limited studies for their use in animals. The mechanism of action for glucosamine is supporting collagen matrix production and chondroitin's mechanism is to minimize collagen degradation. Only one randomized, placebo controlled trial exists for the use of glucosamine and chondroitin in dogs. In this trial, 71 osteoarthritic dogs were treated with glucosamine and chondroitin, carprofen, meloxicam (Metacam®), or placebo. In this study, the use of glucosamine and chondroitin did not show a significant improvement in pain scores. There are no FDA-approved glucosamine and chondroitin formulations available, although there are several over-the-counter products available for both dogs and cats. Pharmacies that choose to stock these products should look for companies that obtain independent verification of quality and make certificates of analysis available upon request.

PRESCRIPTION DRUG MONITORING PROGRAMS

Prescription drug monitoring programs (PDMPs) exist in 49 states, the District of Columbia and Guam (currently, Missouri does not have a PDMP). PDMPs act as a central location for records of all controlled substance prescriptions processed by pharmacies and dispensing practitioners. The primary purpose of a PDMP is to prevent diversion, and records can be accessed by prescribers and pharmacies to query prescription drug history for a patient. PDMPs are administered on the state level by a variety of state agencies including boards of pharmacy, departments of health, professional licensing divisions, law enforcement agencies, and other offices. Some states allow for sharing of data across state lines. Twenty-eight states participate in the Interstate Data Sharing Program. Practitioners and pharmacists in these states are allowed to query records in not only their state, but all states in this program.

PDMPs have greatly improved the way that we track and prevent prescription drug abuse, but they still have their shortcomings, especially when it comes to processing companion animal prescriptions. In most states, if not all, an animal would have their own profile when it comes to the PDMP. Unfortunately, inconsistencies in a pet's information could lead to several profiles. For example, querying the database requires a date of birth. It is common to not know a pet's exact birthday. "Fido Smith" with a birthdate of 1/2/14 at one pharmacy may have a separate profile than "Fido Smith" with a birthdate of 1/3/14 at another pharmacy. Additionally, it is not uncommon for two persons with different last names to own one animal. The same animal could be "Fido Smith" at one pharmacy and "Fido Jones" at another. This again would create two separate PDMP profiles. Furthermore, privacy law makes it difficult to search the PDMP. If presented with a controlled substance prescription for a companion animal and diversion is suspected of the owner, in most cases a query cannot be done on the owner unless that person presents a prescription for themselves. While PDMPs have their problems, pharmacists have long been sleuths when it comes to diversion. Continue to use skills applied to human prescription drugs and search the PDMP when you can.

CONCLUSION

Types of and treatment of pain in companion animals is quite similar to that of humans. Treatment includes a combination of non-pharmacologic, pharmacologic, and adjuvant therapies. With the information reviewed in this article, you should be able to confidently fill a prescription for your longtime customer's German shepherd, as well as provide care for the many four-legged patients you will see in your pharmacy. ■

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Editor's Note: For the list of references used in this article, please contact *America's Pharmacist* Managing Editor Chris Linville at 703-838-2680, or at chris.linville@ncpanet.org.

Continuing Education Quiz

Select the correct answer.

1. Hot packs heat to a depth of:
a. 1 cm
b. 2 cm
c. 4 cm
d. 6 cm

2. What weight loss percentage has been shown to decrease pain scores in dogs?
a. 2-4 percent
b. 4-6 percent
c. 6-8 percent
d. 8-10 percent

3. A dog whose joint movement is manipulated by a veterinarian or a therapist is classified as what type of therapeutic exercise?
a. Passive
b. Assisted
c. Active
d. Mechanical

4. What process uses photostimulation in order to reduce inflammation in deep tissues?
a. Heat packs
b. Active therapeutic exercise
c. Extracorporeal shockwave therapy
d. Therapeutic lasers

5. The World Health Organization (WHO) pain ladder says that pain treatment should start with:
a. Non-opioids
b. Mild opioids
c. Opioids
d. Adjuvants

6. Which of the following is a mechanism by which NSAIDs harm kidneys?
a. Increased sodium excretion
b. Decreased renal blood flow
c. Increased potassium absorption
d. Decreased water diuresis

7. Which of the following NSAIDs is the only one approved for use in cats?
a. Deracoxib
b. Robenacoxib
c. Firocoxib
d. Meloxicam

8. Which of the following is NOT a counseling point to make when instructing an owner on how to give carprofen to their dog?
a. Give with food.
b. Make sure plenty of water is available.
c. Keep out of reach of the dog.
d. Watch for sedation.

9. At what dosage does acetaminophen become toxic to cats?
a. 1 mg/kg
b. 5 mg/kg
c. 10 mg/kg
d. 15 mg/kg

10. In general, cats have a _____ analgesic response to tramadol than dogs.
a. Better
b. Worse
c. Equal

11. Which metabolite of tramadol is thought to be responsible for the majority of tramadol's analgesic effect?
a. O-desmethyltramadol (ODM)
b. N, O-didesmethyltramadol (DDM)
c. N-acetyl-para-benzoquinoneimine (NAPQI)
d. 4-hydroxytryptamine (4-HT)

12. Which of the following is NOT a common adverse effect of tramadol when used in companion animals?
a. Sedation
b. Nausea
c. Salivation
d. Kidney failure

13. Why is the transmucosal route an optimal route of administration of buprenorphine in the cat?
a. A cat's oral cavity is slightly basic, allowing for optimal absorption.
b. A cat's oral cavity is slightly acidic, allowing for optimal absorption.
c. Buprenorphine can exhibit full mu-opioid agonist activity buccally.
d. Buccal administration avoids the ceiling effected demonstrated with other routes.

14. What is the appropriate fentanyl transdermal patch size to give to a 42 kg Labrador retriever?
a. 25 mcg/hour
b. 50 mcg/hour
c. 75 mcg/hour
d. 100 mcg/hour

15. How does amantadine exert its effect?
a. Antagonist of the N-methyl-D-aspartate (NMDA) receptor
b. Agonist at the mu opioid receptor
c. Downgrades voltage-gated calcium channels
d. Enhancement of adenosine and gamma-aminobutyric acid (GABA) receptors

16. Xylitol is a sweetener that is used commonly in commercially available gabapentin suspensions. What is the most common symptom of xylitol toxicity?
a. Hypoglycemia
b. Hyperglycemia
c. Polyuria
d. Polydipsia

17. Which of the following is NOT an adverse effect associated with amitriptyline?
a. Polyuria
b. Polydipsia
c. Hypoglycemia
d. Sedation

18. Based on the randomized controlled trial in 71 dogs with osteoarthritis, what is the best recommendation you could give to an owner regarding the use of glucosamine or chondroitin in their dog?
a. Recommend glucosamine only.
b. Recommend chondroitin only.
c. Recommend both glucosamine and chrondroitin.
d. Recommend neither glucosamine nor chrondroitin.

19. How many states participate in the Interstate Data Sharing Program of their prescription monitoring data program?
a. 10
b. 28
c. 42
d. 50

20. Which dose of carprofen is appropriate for a 75-pound golden retriever?
a. 75 mg twice daily
b. 75 mg once daily
c. 150 mg twice daily
d. 150 mg once daily