

PAIN MEDICATIONS FOR PETS, 101



Pain management is a field of medicine that is changing very rapidly. If a veterinarian hasn't been to any lectures on pain management in the past two years he or she is likely out of date already. Here at Best Friends we work very hard to stay current in this area because one of the basic principles we live by is "Pets should not have to be in pain." The following is our attempt to make sense of a confusing array of medications that our clients are mostly unfamiliar with.

First, some basic principles about pain management:

- **Multimodal therapy** is the norm in pain management today. Pain is very complicated, with multiple pathways, neurotransmitters and receptors. No single pain medication works on all of these pathways. The more severe or chronic the pain, the more likely it will require two or more medications given together to control it. We are trying to interrupt pain pathways to the brain in as many places as we can.
- **It is easier to prevent pain than to get it under control once it is there.** It also takes higher dosages to bring pain back down once it is present. The best pain management preempts the pain, cutting it off before it has a chance to start. This is why we usually have you start your pet's pain medication prior to surgery, and why we use high doses of medication immediately following a painful injury or procedure and then taper down gradually.
- Pet owners get worried when their pet is groggy and "drugged up" but that's normal when a dog or cat is on strong pain medication, just as it is for a human on morphine. Animals can't push the button on the morphine pump so we have to guess at how much medication they need. **It is always better to have a groggy pet who is comfortable than one who is painful.**
- Chronic pain tends to worsen with time, not only because the cause, such as arthritis, is progressive but also because **pain reinforces itself.** The more pain transmitters are used up the harder the body works to replace them and the more become available to trigger yet more pain. With severe pain, even gentle touches can trigger pain because the whole nervous system has been over-sensitized. This is called "ramp up."
- **Drugs are not the only way to address pain.** Cold laser, acupuncture, cold packs and massage are examples of alternative therapies for pain. The best pain control for arthritis is weight loss. Patients usually require far less pain medication if they are of normal weight.

A word about tramadol: we have relied on tramadol heavily over the past ten years but recent research shows that it does not work nearly as well in dogs as we thought it did. It makes them sleepy while not actually making them less painful. We are phasing tramadol out for dogs but most veterinary hospitals have not yet caught up with

Recent research has shown us that tramadol doesn't work nearly as well in dogs as it does in people, because dogs lack the pain receptor that it targets.

us. If your dog has been taking tramadol we will be talking to you about switching to something that works better.

NSAIDs

Non-steroidal anti-inflammatory Drugs, or NSAIDs, have been the mainstay of pain management for decades, not only because they are effective at reducing pain but because they also reduce inflammation. For diseases such as arthritis, we must address the inflammation or it will continue to eat away at the joint cartilage and cause more pain. Inflammation also causes swelling, bruising and redness, so any injury or infection with these signs is likely to be treated with an NSAID. See our separate handout on this class of drugs, or our video on the subject, for more information.

Pet owners may be very leery of NSAID drugs, as there is a lot of negative, false and misleading information about them on the internet. We have been accused more than once of trying to kill someone's pet by prescribing "dangerous" medications. The facts are that dogs taking NSAID drugs such as **carprofen (Rimadyl®)**, **deracoxib (Deramaxx®)** and **meloxicam (Metacam®)** actually have two year longer life expectancies. The risk of liver failure from carprofen is only 1.5 out of every 10,000 dogs. It's untreated pain from arthritis that kills dogs by the millions via euthanasia, not the drugs we use to treat the disease.

A new arthritis drug for dogs called **grapiprant (Galliprant®)** is now available. Grapiprant works similarly to an NSAID but it targets just one specific pain receptor. Other NSAIDs also affect other similar receptors that are important to kidney health and the maintenance of the lining of the stomach, so those drugs have a higher risk for side effects to those organs. The FDA toxicity studies on grapiprant involved giving dogs 15 times the label dose with no fatalities or serious side effects. It should be a great choice for treating chronic pain in dogs who don't tolerate other NSAIDs such as carprofen and deracoxib. Galliprant can be used off label for cats as well.

For cats, we love a different type of NSAID called **Onsior®**. **Onsior® (robenacoxib)** binds to areas where there is pain and inflammation, while staying at a lower level in the bloodstream. This is another way that toxicity from the medication is reduced, making Onsior safer than older NSAIDs such as carprofen and meloxicam. It comes in a small, chewable tablet. Onsior is also available for dogs now. **Meloxicam** is usually our first line drug for acute pain in cats because it comes in an oral liquid that is easy to administer or hide in food, but we are reaching for Onsior more and more because of its safety factor.



Figur

Opioids

Another important category of pain medications is the opioids. This class was originally derived from the opium poppy and includes opium, **codeine and hydrocodone**, **morphine** and its derivatives (**hydromorphone**, **oxymorphone**), and newer forms such as **fentanyl** and **oxycodone (Oxycontin®)**. The drugs in this class most commonly used in dogs and cats are **hydromorphone**, **butorphanol**, **buprenorphine** and **fentanyl**. **Methadone** is being used more in animals as well.

Most people know of methadone only in its role in helping with heroin addiction but it is an opioid pain reliever in its own right.

Tramadol is an opioid as well. It blocks M1 opioid receptors in humans and cats. It also has mild effects on the serotonin and norepinephrine nerve pathways. The reason it doesn't work in dogs is that dogs don't have M1 receptors, a fact discovered only recently. The serotonin and norepinephrine effects can make dogs sleepy but provide very little pain control.

Since we are not using tramadol very much for dogs now, we are relying more on other oral opioids such as codeine and hydromorphone. Unfortunately, these are not absorbed consistently from dog to dog, so they work well in some dogs but not so well in others.

Opioids can cause a variety of side effects but these are rarely serious and almost never fatal except in the case of a massive overdose or long term use. Drowsiness and lethargy are common.



Some cats and dogs experience what is called "dysphoria," sort of the opposite of euphoria. Instead of being blissed out they become restless, tending to pace and pant, which can drive pet owners crazy. Nausea and constipation are occasional problems. Fentanyl can increase appetite, which is a blessing for us when addressing severe pain in cats. Cats on fentanyl tend to be happy and hungry.

For severe acute pain we will likely be reaching for an NSAID and an opioid to use in combination with each other. More and more we are also using gabapentin, a drug that affects many types of nerve transmission, making it useful for treating seizures and anxiety as well as pain (see below).

Chronic pain is different from acute pain and in fact is an entire disease process in and of itself. Even when the original source of pain is removed, for example with a hip replacement, the chronic pain may not resolve. 15-47% of human patients who undergo hip or knee replacement surgery continue to feel pain in the operated joint. Pain can be disabling, to people or pets, even after a technically successful, uncomplicated procedure.

Arthritis and cancer are two processes that can lead to severe, unremitting pain that worsens over time. Dogs can reach bone-on-bone grinding in their joints relatively quickly, as they have only 1-1.5 mm of cartilage lining their joints, compared with 4-5 mm in humans.

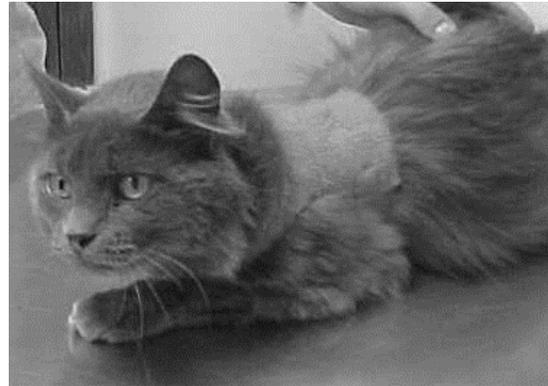
Other commonly used pain medications

Gabapentin is used at a low dose to control seizures, at a moderate dose for pain prevention and antianxiety effects, and at high doses for severe or chronic pain. It frequently causes drowsiness and the higher the dosage, the more likely this will happen. However, the drowsiness

tends to abate as a pet gets used to it. For severe or chronic pain we usually start with a lower dose and gradually increase it, especially for dogs, or they will get too drowsy and sleep all day. This means it takes a few weeks to gradually raise the dose until it's working effectively. While we are doing this, we will be using other medications to tide us over until the gabapentin is working. As pets age, their efficiency at metabolizing gabapentin can wane and side effects may reappear again, especially hind leg weakness. If this happens, we reduce the dosage.

Cats are very tolerant of gabapentin and it has less risk of side effects than many NSAIDs do in felines. Gabapentin is our first choice drug for arthritis in cats and is usually added for dogs once NSAIDs are no longer sufficient to keep pain under control. Many cats will take it mixed in canned food or we can get it in an oral liquid that can be flavored with chicken or tuna. We also stock a plain tablet.

For dogs, it comes in inexpensive, generic capsules. Human pharmacies carry gabapentin, too, but we often can give it to you at a lower price than a human pharmacy will. A human oral syrup is available and can be used in cats short term but it contains xylitol, which is highly poisonous to dogs.



Another drug we are reaching for more often is **amantadine**, which is most effective for nerve pain and for "ramping down" severe, chronic pain. For slipped discs, spinal injuries, amputations, diabetic neuropathy or burns, it can be a wonder drug. For severe arthritis it is usually used for 3-4 weeks to break the pain cycle and ratchet it back a few notches so that we can then keep the pain under control with our other therapies. Amantadine works well to fill the gap until gabapentin starts working.

Acetaminophen (Tylenol®) is being used more frequently in dogs, either as an adjunctive to other arthritis medications or in combination with codeine. Acetaminophen can be toxic to the liver in people, and is deadly to cats, but it is very safe in dogs.

Our goal in pain management is always to enable your pet to regain normal activities of daily life (ADLs). We want your dog or cat to be able to do what they love to do. Let's get started!

Your pet's pain management plan is:

Caring People Helping Pets

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Pain management for surgical or dental procedures

As we mentioned in our list of important points on page one of this handout, preventing pain before it starts is the goal. Most of our patients coming in for painful procedures have already been started on oral medication prior to surgery. We want it in the pet's system at least 24 hours prior to the procedure. This will usually be **carprofen** (an NSAID) for dogs and **gabapentin** (not an NSAID) for cats.

The exception to this rule about starting medication ahead of time is the use of NSAID drugs in cats. Cats are most likely to have kidney damage from NSAIDs when their blood pressure or temperature drops below normal. Since anesthesia commonly causes these effects we wait until after surgery to administer an NSAID for short procedures on cats, such as neutering. We rely on local anesthetics to provide pain control initially.

Hydromorphone given by injection is the most common pain medication used for dogs before surgery or dentistry. It provides good pain control for about 4-5 hours and it is mildly sedating. It can be used in combination with other drugs for greater sedation or as part of a general anesthesia protocol.



In cats, we are more likely to use the milder opioid **butorphenol** prior to surgery and buprenorphine afterwards. **Buprenorphine (Buprenex®)** can be given as a single injection that lasts 6-12 hours, depending on the dose, or it can be followed up with an oral form or a 72 hour long-acting injection. Most cats do very well on buprenorphine but a few become agitated from it.

The original study done on buprenorphine in cats showed it was very well absorbed from the mucous membranes that line the mouth but a subsequent study done using a different methodology showed that only about 30% of what is given orally actually makes it into the bloodstream. The dosages we use here at Best Friends are based on this more recent study and are much higher than you may see used elsewhere. This is to make up for the fact that it is not really as well-absorbed as was originally thought.

Buprenorphine works well for small dogs, too, but it is prohibitively expensive for large ones. Dogs are more likely to go home on oral **hydromorphone** or **codeine**. We often give a higher dose of carprofen for the first three days after major surgery as well. For orthopedic procedures we will usually taper slowly off pain medications one at a time as the pet heals. There is a lot of variation from dog to dog as to how much pain medication is needed and for how long.

Fentanyl is another opioid we use frequently. It is given intravenously for short duration pain control during surgery. For pain control lasting 3-5 days it is applied in a patch form. We use Fentanyl patches frequently in cats and occasionally in dogs. It comes in a topical gel for dogs as well, although so far the gel has remained very expensive.

Ketamine has been used in veterinary medicine as an anesthetic drug for at least forty years. More recently, it has been used at much lower dosages to reduce pain, especially in combination with morphine and lidocaine. A new study shows that adding a little ketamine to every liter of fluids we administer IV during procedures can reduce pain, not only during the procedure but for hours afterwards. If we let the IV fluids drip tiny amounts of ketamine for 6

hours while a pet is here in the hospital, let's say for a dental extraction. The pain control persists for another 12 hours after the pet goes home! 18 hours of ketamine CRI (continuous rate infusion), for example while a dog is hospitalized for ACL surgery, provides 72 hours of pain control! Needless to say, from now on if your cat or dog is having a painful procedure done here at BFVC there will be ketamine in the IV fluids.

Another drug we use for both anesthesia and pain control is **Dexdomitor® (medetomidine)**. It is used for short procedures where both pain control and sedation are needed; in combination with opioids and ketamine for general anesthesia; and in small amounts for pain control or to relieve anxiety. One of the nicest things about Dexdomitor is that we can reverse its effects, so we can wake a pet up when a procedure is over or if the pet has unwanted side effects.

Local anesthetics are underused in both human and veterinary medicine. **Lidocaine** and its sister drug **bupivacaine** are actually the most effective pain medications we have, because they prevent pain from ever getting started in the first place. In people, local anesthetic used along an incision line is still keeping the incision comfortable a week afterwards.

Here at Best Friends, we use local anesthesia for almost every surgery and dental extraction we do. A new form of bupivacaine, lasting 72 hours, will be great for keeping pets comfortable following major surgery, such as a TPLO for a torn ACL. We won't need to rely so much on stronger systemic drugs if we can simply numb an area for a few days. Less sensation from an incision also means less licking or chewing at it.

After surgery or dental work, *you* are in the best position to look for subtle changes in behavior that indicate your pet may be in pain – but pain doesn't always look like what owners expect and animals are very good at hiding pain. Please see our handout titled "How to Tell if Your Dog/Cat is in Pain" for more information on what to watch for.

We have carefully chosen the most appropriate pain medication and the duration of treatment based on the level of pain expected for the procedure your pet had done. **Please administer all the medication as planned. We don't want you to see any pain symptoms – if we have managed post-operative pain properly you should not see signs of pain at all!**

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Other adjunctive pain medications

We all would like chronic pain to be something easily corrected. Unfortunately, it's not, and what works well for one patient may not work well for another. Most patients, human or animal, do best when several medications are combined. It may take weeks or a few months to nail down the combination that works best for your individual pet.

For any type of pain expected to be long lasting we recommend omega 3 fatty acids (fish oil). Glucosamine is almost always added in for arthritis. For more information on supplements, see our separate handout.

Rehabilitation is also used for many types of pain, both acute and chronic. Therapy laser treatments, acupuncture, dry needling and underwater treadmill therapy are all frequently recommended. We also have separate handouts on these therapies.

There are many drugs and supplements that are used less commonly for severe or chronic pain. When we are frustrated and not controlling pain well enough with our regular cocktails of drugs we will start adding in some of these. Many of them were used first for other purposes but have been found to decrease pain as well. Some are used for specific types of pain, e.g. osteoarthritis, neck and back pain or cancer pain. Several are used in humans as antidepressants. Medications that affect brain chemicals can work for both depression and pain. The following is a not-so-brief list of some of the things we are beginning to use more of.

Probiotics: Keeping the gut balanced and healthy with probiotic bacteria improves immune system function and helps to relieve chronic pain as well.

Antidepressants: Tricyclic antidepressants (TCAs) such as amitriptyline as well as serotonin-norepinephrine reuptake inhibitors such as Cymbalta™ and Effexor™ can be effective as pain medications. Generics are available, which makes the price pretty reasonable to try. They are especially useful for treating cancer pain.

Apoquel: This is our primary anti-itch drug used for allergies in dogs. The Janus-kinase receptors it targets are involved in pain sensation as well as itch.

Cannabinoids: Marijuana derivatives such as CBD can work well for many types of pain. Right now, they are completely illegal in Wisconsin but that may change in the next few years. Many products are available on-line but

Cerenia™ (mirtazapine): This is our primary anti-nausea drug and it also reduces abdominal pain with efficacy similar to morphine.

Doxycycline/minocycline: These drugs are antibiotics that also have anti-inflammatory effects, especially inside joints and muscle tissue. They can also be quite helpful for osteosarcoma (bone cancer).

Melatonin: Melatonin is a hormone produced in the brain that regulates sleep/wake and seasonal cycles. It is used for jet lag in humans, for disruption of hair growth in dogs and ferrets, as well as for anxiety and pain relief. It is especially helpful for cancer pain. It is very inexpensive.

Mexiletine: This is a drug primarily used for certain types of heart disease. It's like an oral version of lidocaine, which is a sodium channel blocker. Sodium channels are important in conducting signals between cells – pain signals as well as electrical signals in the heart muscle.

NV-01 (for dogs) & NV-02 (for cats): These drugs are currently in development and are expected to come out in 2018 or 2019. They are antibodies that bind with a chemical messenger called nerve growth factor or NGF, which is important in osteoarthritis. They will be available in the form of a monthly injection. So far, no side effects at all have been reported, so they sound very promising.

Piroxicam: Piroxicam is an older NSAID drug that works particularly well for bone cancer and bladder cancer. It does not have the high safety profile of newer NSAIDs, so it has higher risk of causing gastric ulcers. If your dog is taking piroxicam we may need to stop giving it for a time periodically, just to give the stomach lining a break to repair itself.

Prednisone/prednisolone: These steroid drugs can reduce pain and inflammation from many different types of cancer.

PEMF: Pulsed electromagnetic fields therapy is safe and effective in improving arthritis pain. It is also used to speed bone healing after fracture repair and to induce faster healing after nerve damage. It works by stimulating calcium (Ca) to transform into a molecule called calmodulin (CaM). This transformation is a voltage-dependent process, which is why an electromagnetic field can stimulate it. CaM then triggers a natural anti-inflammatory cascade within cells. You would rent our Assisi loop device, which your dog would wear for 15 minutes or more per joint per day for a month at a time. The loop is used for the stifle (knee), where it wraps around the leg. Velcro wrap vests hold the device in place for use on shoulder or hip joints.

Pamidronate™ (bisphosphonate): For bone cancer pain, bisphosphonates are our best tool to use in addition to oral pain medication. These are drugs that were developed for treating osteoporosis in humans. They provide long-lasting bone pain relief. They stimulate fracture healing, too, so even a broken bone cancer-affected leg will heal with treatment. Bisphosphonate is administered intravenously here in the hospital once a month or so.

Intra-articular injections: It is very common to inject steroids in the joints of humans with arthritis. We also can do this with dogs. We usually use a combination of triamcinolone (the steroid part) and hyaluronic acid (which is a component of joint fluid and cartilage). Steroid injections degrade cartilage so they are rarely used unless the cartilage is already eroded away. The hyaluronic acid helps to counteract the degradation of cartilage from the steroid injection.

Osteosarcoma treatment facts:

OSA is one of the most painful forms of cancer. We will attack that pain very aggressively in order to provide decent quality of life.

Amputation without chemotherapy leads to faster growth of metastatic tumors in the lungs. Leg amputation should always be followed by chemo.

Median survival after amputation & chemo is 8-12 months, with 20% of patients living two years. Adding the new cancer vaccine Her-2/neu extends survival to an average of 956 days!

Another product you may be surprised to hear can be injected into a painful joint is Botulinum toxin, or Botox™. Botulinum toxin injections into the joints have shown a long-lasting benefit in human end-stage osteoarthritis patients. Consistent pain reductions and improvements in function have been sustained for 6 to 12 months or more after injection and we can repeat the treatment again as the effects wear off. A single (expensive) vial of Botox will treat two joints.

Stem cell therapy: Stem cells can be harvested from fat and then injected back into the dog, either into the affected joints themselves or into the bloodstream, where they tend to target damaged tissue and end up back in the joints that way. The idea is that the stem cells will transform into cartilage-producing cells that will rebuild the inside of the joint.

Two anesthetic procedures are needed for a stem cell transplant, one to harvest the fat and the second to inject it into the joints. Fat can be harvested and banked for later, so we could acquire fat tissue during a spay, neuter or other routine procedure and save it until it's needed. Injections can be repeated later (usually 1-2 years later) using the same stem cell bank created previously. Stem cell therapy is very expensive to do and there is not enough research yet to prove it works. We would consider it a salvage procedure when nothing else has worked.