Building a Chronic Pain Management Pyramids for Cats

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When building the chronic pain management pyramid, begin at the beginning with a thorough examination, including a neurologic exam, soft tissue palpation, joint ROMs, and gait assessment. Perform a metabolic profile so as not to miss important co-morbidities. And don't forget radiographs when they are indicated so as not to miss an obvious OSA and treating it as an OA. Be sure to treat the treatable - - and treat all the treatable. Make a plan and work the plan because chronic pain is best addressed from a MULTIMODAL approach. It is no longer appropriate simply to throw an NSAID at the patient.

We need to break the pain cycle as quickly and effectively as possible before initiating physiotherapy and/or tissue manipulation. Multimodal management of chronic pain means multi-tasking - - think "plate spinning" or juggling. The client is an absolutely essential partner in the process, or the process is doomed to fail. There is no one right answer, but we need to set priorities (and there may be multiples) based on the needs of each individual patient.

Perform your pain palpation systematically and the same way each time. Use 4kg of pressure at each palpation site, and use the fleshy part of P3 (NOT the fingertip). Begin in the paraspinals at the base of the occiput and proceed to the base of the sacrum. Palpate the paraspinals at approximately each spinal segment. Palpate the circumference of the body at the base of the neck by the hands of the clock - - 10 & 2, 9 & 3, 8 & 4. Palpate caudal to the scapulae at those same "clock" points. Palpate at the T/L junction as well. Next palpate the lateral lumbar muscles segment by segment. Then palpate the iliopsoas muscle bundle starting at the T/L and proceeding to the L/S. Squeeze the proximal quadriceps between the flat of the thumb and the lateral index finger. Perform joint ROMs from toes to torso. Once through the whole body, return to the areas exhibiting a reaction and evaluate with additional palpation and/or ROM to better identify and characterize the presence and nature of pain. Teach/drill/practice and include the entire staff.

Most chronic pain patients are less active, and consequently are overweight. Dr. Denis Marcellin-Little does a great presentation articulating that the most important physiotherapy treatment for chronic pain patients is normalizing body condition. Make a long- term nutritional plan right at the beginning. If a co-morbidity exists, plan for appropriate therapeutic nutrition once weight loss is achieved. Therapeutic nutrition is best achieved with a fixed formulation and consistency of feeding.

Break the pain cycle pharmacologically. NSAIDs remain one cornerstone of chronic pain management, particularly in the initial stages. They decrease inflammation and provide analgesia by acting at various locations within the nervous system. Once pain is controlled, we can (and should) titrate the dose to lowest effective dose, and that may be 0. Once removed, the NSAID can then be reserved for use as an inflammatory pain flare. Do not "mix & match" NSAIDs.

Chronic pain is "maladaptive" pain (see Clifford Woolf) or "maldynic" pain (see James Giordano). Maladaptive pain demands we target the dorsal horn of the spinal cord. "Targeted therapy" is a relatively new concept in human pain management, and a REALLY new concept in veterinary medicine.

Gabapentin affects α-2-δ subunit of the calcium channel in the dorsal horn of the spinal cord. It is an important gold standard for chronic, maladaptive pain management in humans, and it is emerging with a perioperative role. We need to dose **appropriately** at 5 – 15 mg/kg BID – TID to **start.** You will see drug activity within just a few days and maximal effects within 7 – 10 days. DO NOT reduce the dose too quickly or you will risk rebound pain. Begin your dose reduction following at least several months of stability. Long-term dosing is fine - - there are no liver or kidney issues to worry about. Sedation is the dose-limiting side effect. If sedation occurs, **do not** discontinue gabapentin - - simply reduce the dose and proceed with your plan. This drug has non-linear pharmacokinetics which makes the dose escalation very different from any other drugs we generally reach for. Evaluate the patient, calculate the dose, and begin with the BID dose given ONCE daily in PM for 3 days, then give the dose BID (e.g. 50mg PO once in PM for 3 days, then 50mg PO BID). Reassess the cat in 10 – 14 days. If it is still painful, increase the dose (e.g. 50mg PO TID). Reassess again in 10 – 14 days. If the cat is still painful, increase the dose again (e.g. 100mg PO BID). Once the cat is comfortable stick to that dose for a minimum of 4 – 6 months before beginning de-escalation of the dose, and DO NOT be in a hurry to de-escalate. I actually NEVER do... The first dose de-escalation should come a MINIMUM of 4 - 6 months after stabilizing the cat's pain at the lowest level. Decrease the dose, then recheck in 2 – 3 weeks to look for breakthrough pain. The next de-escalation should come in 2 – 4 months, recheck in 2 – 3 weeks for breakthrough pain, etc. Repeat the cycle on this interval. If the pain returns, simply increase the dose - - e.g. 100mg PO BID, then decrease the dose to 50mg PO TID, then decrease to 50mg PO BID, etc. Just a reminder, I NEVER decrease or eliminate gabapentin in my chronic feline pain patients.

Amantadine is an NMDA receptor antagonist that complements NSAIDs and gabapentin. We only have data for dogs, but I use this drug as an adjunct in cats routinely. We use 2 – 5 mg/kg/day. It is exceptionally well tolerated long-term compounding works great.

Tramadol is useless and should not be used... period.

Adequan® is VERY useful in cats with OA. This reflects extra-label usage. Give the injections SQ and NOT IM. Teach clients to dose this at home. Use the canine dosing for cats - - 2 mg/# SQ twice weekly for 4 weeks, then once weekly for 4 weeks, then twice monthly for long-term maintenance. Start using as soon as OA is diagnosed. Long-term use works very well.

As for nutrition and nutraceuticals, follow the evidence - - HPD j/d® Feline, glucosamine/LMW chondroitin/ASU, Omega 3 FA's, Microloactin®.

Microlactin® (Duralactin® by VPL) is a milk protein concentrate from the milk of hyper-immunized cows. Hyper-immune milk factor (HIMF) inhibits inflammation in many animal models. It appears to be effective regardless of the etiology of inflammation and demonstrates no evidence of GI irritation. It works by a different mechanism than NSAIDs or corticosteroids. The first data about the anti-inflammatory activity in milk was disclosed in 1981. The novel activities illuminated from pharmacological studies on THIS molecule include the following:

- Activate macrophages
- Inhibit neutrophil migration
- Inhibit neutrophil adhesion

- Inhibit infection-induced inflammation
- Inhibit arthritis
- Suppress edema (rat model)
- Inhibit auto-immune disease

Microlactin® exhibits a very selective mechanism by blocking cytokines which contribute to the perpetuation of inflammation. It modifies the biological response to inflammation and changes the response of cytokines and neutrophils. It alters the signaling to neutrophils that "calls" them to the sites of inflammation. The neutrophils then do not release the destructive enzymes that perpetuate the inflammatory process. We see much same efficacy profile as NSAID, but the action happens by a different mechanism, so there is no NSAID adverse event profile. Microlactin® can be used safely in dogs, cats, and horses. The dose in cats (per Dr. James Gaynor) is 30 - 50 mg/kg PO BID. It takes time for maximal effects. We see initial effects within 4 – 7 days and maximal effects in 10 – 14 days. This is why Microlactin® is not well positioned for acute pain. For chronic pain, during weeks 1 – 3, overlap with the NSAID, steroid, etc. After week 3, continue Microlactin® for long-term anti-inflammatory activity.

Physiotherapy/physical medicine modalities:

- Heat
- Cold
- Therapeutic Laser
- NMES
- TENS
- Therapeutic U/S
- Tissue mobilization
- Medical massage
- Tui Na (Chinese medical massage)
- Acupuncture
- Chiropractic/osteopathic manipulation
- Myofascial trigger point therapy
- Hydrotherapy
- E-stim whirlpool
- Swimming
- UWT

Be as specific as possible when making your pain management plan. Write everything down and have clients keep an "activities of daily living" (ADLs) diary. Conduct a medication, feeding, nutraceutical review at each visit. Once the patient is comfortable/stable, functional, and strong, you can consider removing some elements of the pain management pyramid.

Change only one thing at a time. Consider at least 1 – 3 months of stability before adjusting medication doses. Begin by reducing the drug with the greatest potential to cause adverse events (generally, this is the NSAID). Titrate dose down to lowest effective dose, and you may want to consider stopping the NSAID and reserving it for acute pain episodes. Reassessments should happen at regular intervals during NSAID dose reductions - - we choose every 2 – 4 weeks. If we reduce/remove the NSAID and pain returns, we return to the next higher dose for long-term use. Next, target gabapentin reduction (see gabapentin details above). Most human patients never eliminate gabapentin, so don't sweat this. We never remove gabapentin, Adequan®, nutritional joint support, or omega 3 FA's.

Keys to success

Create as detailed and personalized a plan as possible
Write everything down
Create realistic expectations in dialogue with the client
Schedule the next reassessment +/- treatment appointment before the client leaves
Review all medications/dosing, feeding/nutrition at each visit
Track medication refills (compliance)
Relish the challenges of chronic pain Involve the entire healthcare team

These will be your most rewarding cases and your most committed clients.

Resources

Veterinary AnaesthesiaSupportGroup
www.vasg.org
American Academy of Pain Management
www.aapainmanage.org
American Society of Pain Educators
www.paineducators.org
AAHA/AAFP Pain Management Guidelines for Dogs & Cats 2015
Download at: www.aahanet.org
ISFM & AAFP Consensus Guidelines: Long-term Use of NSAIDs in Cats Task Force Members: Andrew H Sparkes, BVetMed, PhD, DECVIM, MRCVS Reidun Heine, DVM, PhD, MRCVS B Duncan X Lascelles, BSc, BVSc, PhD, MRCVS, CertVA, DSAS(ST), DECVS, DACVS Richard Malik, DVSc, DipVetAn, MVetClinStud, PhD, FACVSc, FASM Llibertat Real Sampietro, DVM Sheilah Robertson, BVMS (Hons), PhD, CVA, DACVA, DECVAA, MRCVS Margie Scherk, DVM, DABVP (Feline Practice) Polly Taylor, MA, VetMB, PhD, DVA, MRCVSDownload at: http://jfm.sagepub.com/content/12/7/521.full.pdf+html

Non-Pharma Options for Feline Pain: Nutrition, Nutraceuticals, and Rehabilitation

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For pain in animals, pain is what ***WE*** (humans) say it is. There is tremendous individual variability among both patients and observers. There is not one "right" answer. Pain is complex and scientifically intriguing, clinically challenging, and easy to overlook (especially in cats). For us to improve the treatment of feline pain, it means making changes in what we currently do..

The fundamentals of chronic pain management mean understanding that treating pain is good medicine, and that multi-modal management is the strategy of choice. The most common application of nutrition & nutraceuticals in pet pain is among feline patients with chronic maladaptive pain. These are the patients who benefit most from a multi-modal approach to their pain. OA is the number one cause of chronic pain in cats – approximately 20% of dogs AND CATS across ALL ages have OA. One study reveals that 90% of cats over 10 years of age have radiographically evident OA. Market research reveals that approximately 30% of dog owners identify bone and joint problems as an issue, and it is the 7th most common canine claim submitted to VPI®. Feline claims lag due to the difficulty of identifying feline patients in pain.

Food/nutrition

Putting together a multi-modal pain management strategy for a cat is like building a pyramid with a firm, broad foundation. Our patients need to eat something every single day, so nothing is easier than prescribing daily intake that makes a positive contribution to medical care and patient well-being. Weight loss and management are the single most important adjunctive pain management tools for chronic/maladaptive pain, and are acknowledged as the most critical physical rehabilitation techniques as well. Overweight and obesity impact joints with OA and increase the severity of OA symptoms. Weight loss alone has been demonstrated to decrease the risk of OA development, slow the progression of existing OA, and to relieve pain from OA - - excellent studies in humans, and ongoing studies in animal patients. Clinically, these ideas ARE being born out in canine and feline patients.

For weight loss success we MUST follow the science to recommend the best nutrient profile for the job. Clients need to be educated that over-the-counter pet foods will NOT do the job. Clients do NOT understand that OTC diets labeled "light" are NOT significantly calorie-restricted. This means well-intentioned pet owners are seduced by marketing to believe they are doing something useful for the pet. Our obligation is to educate our clients so that they may make FACT-based decisions, not FANTASY-based decisions. At the moment, Hill's Prescription Diet Advanced Metabolic Weight Solution provides the strongest science coupled with the strongest/best results for body condition normalization.

Prescribe SPECIFIC meal size AND frequency, and DO NOT BE DECEVED BY THE "FEEDING GUIDE" PORTIONS! The portions therein are ALWAYS too high to achieve the necessary results. Prescribe a

SPECIFIC snack list. Clients WILL "snack" their pets, so consider green beans, broccoli, cauliflower – fresh or frozen (NOT canned). These are Point® value "0" in the Weight Watchers® point system.

Schedule no-charge weigh-in appointments with the client and pet at 3 – 4 week intervals. Make the next weigh-in appointment at each scheduled weigh-in or other assessment. Pain patients will be presented for regular pain reassessments, so their weight should be recorded at each of these visits as well.

Consider interactive food toys and dishes for kibble delivery to slow down eating. Have your long-term nutritional profile in mind when embarking on this weight-loss strategy to transition once weight is normalized. Muffin tins make GREAT and CHEAP interactive food toys for cats.

Remember that our genetic profile lays the foundation for our physical reality, health, wellness, and potential to develop disease. The EXPRESSION of a genetic trait is influenced by interaction between the genome and environmental factors. We now know that food/nutrition is one of the most important environmental factors that influence genomic expression. Nutrogenomics is the science of how nutrients affect health at the genomic level, and nutrients serve as dietary signals to the systems that influence gene and protein expression. Step one is to determine the genomic expression difference between healthy and diseased individuals, and step two is to identify nutrients/nutritional profiles that alter genomic expression in the diseased individuals to more closely resemble the healthy individuals. Controlled studies can confirm the anticipated outcomes.

The future of nutrogenomics promises identifying genomic differences in aging and certain disease processes. Research is underway to identify which nutrients can influence genomic expression in beneficial ways. Think of these as "functional foods". This science raises interesting questions/possibilities about our future ability to manage or even prevent disease via "functional foods". Will drugs become obsolete?

We also have a nutritional opportunity to interrupt the progression of OA. OA progression creates a cascade of events and effects: Physical stress on joint – chondrocyte damage – activates degradative enzymes – cartilage matrix damage – structural failure

We need to interrupt the degradation. EPA helps control joint inflammation & blocks degradative enzymes. Research demonstrates the down-regulation of the genes responsible for cartilage degradation with high levels of EPA. A low ratio of omega- 6/omega-3 FAs reduces inflammation in and around joints. A joint support nutrient profile should have several important characteristics including:

- High levels of EPA
- High levels of ALA (EP A precursor)
- Low omega-6/omega-3
- L-carnitine (maintain optimum body weight)

Make a long-term nutritional plan at the beginning and articulate the plan in the medical record and to the client right away. Keep these patients on the radar to keep them on track nutritionally. Follow the science and evidence when choosing nutritional profiles for painful patients, and don't forget to consider any and all relevant co-morbidities when choosing your nutrient profile. Some painful patients have metabolic issues that "trump" their joint disease. Should the patient have a metabolic profile that precludes using a joint-

support food, you can still pay attention to joint health via nutraceuticals and a disease modifying agent (e.g. PSGAGs)

PSGAGs

Adequan® remains the gold standard (NOT the equine formulation) of PSGAGs. PSGAGs are DMAOs – disease modifying agents of osteoarthritis – made from an extract of cow lung and trachea that is then sulfated. They provide the body with the building blocks of cartilage – molecules that bind to cartilage components. The exact mechanisms of action are not completely known, but PSGAGs have indirect anti-inflammatory effects. They assist the body in the repair of cartilage damaged by the consequences by OA and work best when the body is still in motion and the joints are still in use. This reflects extra-label use in cats - - 2 mg/# SQ 2 X per week for 4 weeks, weekly for 4 weeks, then twice per month indefinitely.

Omega 3 FAs

There is clear evidence that high levels of EPA accomplish two important functions in the joint – decreasing inflammation in and around the joints, and down-regulating the genes responsible for the degradative enzymes that lead to cartilage damage. Flax seed oil is NOT an effective source of EPA for cats. EPA and DHA are both found in fish oil. We need to supplement EPA/DHA (both are omega-3s) at a high enough level to "bottom-load" the omega-6/omega-3 ratio to reduce inflammatory mediators. There is a wide range of canine doses quoted - - 20 – 75 mg/kg/day EPA - - I use the same dosing range for cats because we do NOT yet have the same level of high quality data for cat joints. Based on OA studies, we use 50 - 75mg/kg/day PO of EPA divided BID. Both Nordic Naturals® Omega-3 Pet oil (138 mg/ml EPA) and Nutramax® Welactin (125 mg/ml EPA) are manufactured in alignment with pharmaceutical standards. We need to be able to count on specific mgs of EPA and DHA per dosing unit (capsule or ml). Currently no capsules are available for pets with a high enough concentration of EPA/DHA to make dosing reasonable. Most cats are willing to have these liquids top-dressed on their portion-fed kibbles.

The research is very compelling about the general anti-inflammatory effects of omega-3 FAs, although the human research is more advanced and broad-based than the current published studies in dogs/cats. In human arena, cardiovascular benefits, immune system support, joint health, renal disease, cancer, dermatology, allergies, cognitive function, neuropathy, and possibly diabetes mellitus. Check out www.omega-research.com.

Please forgive the canine emphasis of the following studies:

Roush J, Dodd C, Fritsch D, et al. Multicenter veterinary practice assessment of the effects of omega -3 fatty acids on osteoarthritis in dogs. J Am Vet Med Assoc. 2010;236(1):59-66. Conclusion: Ingestion of the test food raised blood concentrations of omega-3 fatty acids and appeared to improve the arthritic condition in pet dogs with osteoarthritis.

Roush J, Cross A, Renberg W, et al. Evaluation of the effects of dietary supplementation with fish oil omega-3 fatty acids on weight bearing in dogs with osteoarthritis. J Am Vet Med Assoc. 2010;236(1):67-73. Conclusion: At least in the short term, dietary supplementation with fish oil omega-3 fatty acids resulted in an improvement in weight bearing in dogs with osteoarthritis.

Fritsch DA, Allen TA, Dodd CE, et al. A multicenter study of the effect of dietary supplementation with fish oil omega -3 fatty acids on carprofen dosage in dogs with osteoarthritis. J Am Vet Med Assoc. 2010

Mar 1;236(5):535-9. Conclusion: Results suggested that in dogs with chronic osteoarthritis receiving carprofen because of signs of pain, feeding a diet supplemented with fish oil omega-3 fatty acids may allow for a reduction in carprofen dosage.

Budsberg SC, Bartges JW. Nutrition and osteoarthritis in dogs: does it help? Vet Clin North Am Small Anim Pract. 2006 Nov;36(6):1307-23, vii - - "...nutrition has become an integral part of (OA) management. This article focuses on the role and dietary ingredients in OA, evaluating current evidence for obesity management, omega-3 fatty acids, and chondromodulating agents..."

Hansen RA, Harris MA, Pluhar GE, et al. Fish oil decreases matrix metalloproteinases in knee synovia of dogs with inflammatory joint disease. J Nutr Biochem 2008;19(2):101-8. Conclusion: ...results suggest that dietary fish oil may exert beneficial effects on synovial fluid matrix metalloproteinases (MMP) and tissue inhibitors of MMP-2 (TIMP-2) equilibrium in the uninjured stifle of dogs with unilateral CCL injury.

The future of omega-3 FAs remains ahead, and nearly daily, new studies are published about the importance of omega-3 FAs in both wellness and preventing illness. There is more research in store for animals patients.

Microlactin

Microlactin is a milk protein concentrate from the milk of hyper-immunized cows – hyper-immune milk factor (HIMF) – and inhibits inflammation in many animal models. It appears to be effective regardless of the etiology of inflammation with no evidence of GI irritation. It works by a difference mechanism than NSAIDs or corticosteroids, and the first data about the anti-inflammatory activity of milk was disclosed in 1981. Pharmacological studies have illuminated the following microlactin actions:

Activate macrophages, inhibit neutrophil migration, inhibit neutrophil adhesion, inhibit infection-induced inflammation, inhibit arthritis, suppress edema (rat model), inhibit auto-immune disease

Microlactin appears to have a very selective mechanism that blocks cytokines which contribute to the perpetuation of inflammation. It modifies the biological response to inflammation by changing the response of cytokines and neutrophils. It alters the signaling to neutrophils that "calls" them to the sites of inflammation. Neutrophils then do not release the destructive enzymes that perpetuate the inflammatory process. While it exhibits much the same efficacy profile as NSAIDs, it employs a different mechanism, so it does not share the NSAID AE profile.

Microlactin can be used safely in dogs, cats, and horses, and the dose range in dogs and cats is 30 - 50 mg/kg PO BID. It takes time for maximal effects – initial effects are generally seen within 4 – 7 days with maximal effects at 10 – 14 days. During weeks 1 – 3, overlap it with the NSAID or steroid. After week 3, continue microlactin for long-term anti-inflammatory activity.

Glucosamine/Low molecular weight chondroitin

We are still waiting for evidence of definitive benefits from glucosamine to be demonstrated in controlled, well-designed clinical trials. Low molecular weight chondroitin may have a positive effect in a percent of patients, but unfortunately, we cannot predict who will and who will not respond. In 2006, the results were published from the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT) - - see the NIH website. This was the first large-scale, multicenter clinical trial in the US to test glucosamine and chondroitin sulfate

for knee osteoarthritis. It evaluated glucosamine and chondroitin sulfate separately and in combination and was coordinated by the University of Utah, School of Medicine. The study was designed to test short-term (6 months) effectiveness of glucosamine and chondroitin sulfate in reducing knee OA pain in a large number of participants.

Key results - - the positive control (celecoxib) provided statistically significant relief. Overall, there were no significant differences between other treatments and placebo. A subset of subjects with moderate-to-severe pain reported statistically significant relief with glucosamine combined with chondroitin sulfate compared with placebo. Researchers considered these findings preliminary and recommended confirmation through further studies. For participants with mild pain, glucosamine and chondroitin sulfate together or alone were not effective.

This reflects the veterinary experience as some patients some seem to benefit, others do not. Be mindful of your recommendations. Low molecular weight chondroitin may be the key for the "responders". Provide follow-up to modify your plan if this tool is not effective.

Avocado unsaponifiables (ASU)

ASU is an extract made from avocado and soybean oils and has been shown in clinical studies to have beneficial effects on OA. In two studies over 3 months (knee & hip OA), the results revealed that patients who took ASU daily decreased their NSAID use. ASU took at least two months for improvement, but in the long-term studies there were no positive results. Are we seeing improved joint structure versus pain relief? Clearly more long-term studies are needed.

ASU seems to complement effects of other ingredients. For example, ASU plus LMW chondroitin may be more effective than glucosamine and LMW chondroitin sulfate alone at decreasing the expression of several inflammatory mediators.

Pro-inflammatory gene expression in chondrocytes and monocyte/macrophages is inhibited by the combination of avocado soybean unsaponifiables, glucosamine, and chondroitin sulfate, Au RY, Au AY, Rashmir-Raven AM, Frondoza CG, Proceedings, 34th Annual Conference Veterinary Orthopedic Society 2007,57.

There has been an explosion of information within past decade, yet our understanding of all these complex factors still in its infancy. The preliminary science is very exciting because it means more and more "tools" for our pain toolboxes! Be careful to make data-driven recommendations, and stay tuned!

Rehabilitation

Fortunately for cats, ALL of the rehabilitation techniques that we use in dogs can (and SHOULD) be adapted for use in cats. This INCLUDES the use of hydrotherapy in the underwater treadmill. Don't be bashful about utilizing any and all of the most commonly leveraged rehabilitation techniques - - cryotherapy, moist heat, stretching, ROM, joint mobilization, hydrotherapy, therapeutic laser - - for painful cats who can benefit. Tailor your treatments to fit the cat's needs and the cat's preferences.