Natural 'Drugs' for Your Pain Management Toolbox

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Known as supplements, 'nutraceuticals', and phytomedicinals, plant/animal-based therapies are not regulated by the United States Food and Drug Administration (FDA). Thus, unlike pharmaceuticals, manufacturers are not required to provide scientific information to legal authorities for approval. However, supplements are widely used, and many compounds in supplements may be effective. A further complication is in proving the efficacy of supplements; there is the suggestion that it is the interaction of various compounds found in natural substances that generate the clinical effect. This creates a very complicated situation for research, as compared to a single-ingredient pharmaceutical product. Some data is emerging, as companies are motivated by a growing desire for more stringent criteria to produce studies. Unfortunately, many of these continue to be low-quality, without consistent evaluation methods and with varying products/doses, and nearly all with a possible funding bias (paid for by the companies promoting the product) (Bhathal 2017). It is also important to realize the very significant placebo effect attached to non-pharmaceutical interventions, which general further complicates the interpretation of various clinical studies performed to date. In this lecture, we will review the common supplements embraced for pain management (mostly directed at OA), with a balance of possible benefits (often anecdotal or *in vitro*), alongside the presence (or absence) of evidence based medicine (EBM).

Glucosamine/Chondroitin/MSM

Chondroitin is generally produced as chondroitin-sulfate salt. It is intended to inhibit destructive enzymes in joint fluid and cartilage, halt the degradation of cartilage, and with the sulfate, provide essential building blocks for chondrocytes. Glucosamine is sea-life based (lobster, shrimp and crab-shell based) and regulates the synthesis of collagen in cartilage, and may provide mild anti-inflammatory effects. Together, the two nutraceuticals promote the synthesis of glycosaminoglycan and proteoglycan, which are building blocks for the formation of cartilage, protect against synovitis and cartilage degeneration, and modulate metabolism of articular cartilage. *In vitro* results on cartilage are more promising than *in vivo* studies have been, across all species. Some of this may be related to absorption, as glucosamine HCl and chondroitin sulfate require 10 to 20 times the quantity used in *in vitro* studies to reach a plasma concentration that will result in biological activity (Comblain 2016). The glucosamine salt generally used in veterinary products has not been shown to be as well absorbed as the crystalline form, in humans (Bhathal 2017). Many veterinary products are available, and many are combined with other products. This tendency to combine complicates the interpretation of the various studies, as is can be unclear which ingredient mediates the clinical effects (or perhaps, it is the interaction of various ingredients?) MSM is essentially a source of sulfur (duplicate if the chondroitin is bound to sulfur) which is thought to be an important nutrient in cartilage health. MSM has moderate evidence for OA mitigation in humans (Ameye 2006).

Data supporting using it for pain in humans is mixed, but perhaps a bit stronger recently, with a Cochrane meta-analysis showing that most studies are still low-quality but that chondroitin (alone or in combination with glucosamine) was better than placebo (small to moderate effect) in improving pain in participants with osteoarthritis. The conclusion was that the "combination of

some efficacy and low risk associated with chondroitin may explain its popularity among patients as an over-the-counter supplement" (Singh 2016). Three review articles summarize data for use in dogs and cats, and none can conclude efficacy or lack of efficacy (Vandeweerd 2012; Bhathal 2017; Comblain 2016). However, the safety of these products has generally outweighed the lack of data, as described in the conclusions of the Cochrane study.

- Drug Interactions and Toxicity

Benign - possible mild GI effects, and allergy to ingredients or formulations (glucosamine is sea-food based). Possible concerns with anti-coagulants and anti-hyperglycemics (in humans).

- Dosing

Glucosamine ≥25 mg/kg. Chondroitin ≥15–20 mg/kg. MSM >10 mg/kg (Shmalberg 2014).

Hyaluronic Acid (HA)

HA is a high molecular weight glycosaminoglycan that is important in joint fluid, bladder lining, wound healing, etc. In theory, it is the end-product of chondroitin/glucosamine supplementation. It is administered by intra-articular or intra-vesicular (bladder) routes. Oral products are available. In contrast to a 2008 study, HA does not appear to be absorbed orally (Laznicek 2012).

Lipids

Omega Three Fatty Acids

EPA, DHA and ratios. For more detail, see this peer-reviewed, open-access review of ACVN recommendations by Dr. Lenox: http://todaysveterinarypractice.navc.com/role-of-dietary-fatty-acids-in-dogs-cats/ (http://todaysveterinarypractice.navc.com/role-of-dietary-fatty-acids-in-dogs-cats/).

Fatty acids are phospholipids, and are classified as short-chain (<8 carbons), medium chain and long-chain (>12). The presence of double bonds (>2) identify these as poly-unsaturated (PUFA), and the location of the double bonds create the naming (omega-3, 6 or 9). Omega 6 are from animal tissue, sunflower and safflower oils (linoleic acid, arachidonic acid). Omega 3 are from marine and plant sources (Alpha-lipoic acid *ALA, eicosapentaenoic acid *EPA and docosahexaenoic acid *DHA) (Lenox 2016). PUFAs are important mediators of inflammation, with the omega-3s being shown to reduce inflammation is OA, cancer, hyperlipidemia, cardiac, dermatologic, retinal and neurological diseases.

Dogs and cats cannot produce enough omega-3 or omega-6 fatty acids on their own, and require supplementation. Ratios between omega-6:omega-3 supplements have not been found to be important. Omega-6 sources are far more diverse, so supplemental focus falls on the omega-3 fatty acids. Furthermore, unlike humans, dogs and cats do not convert ALA to EPA or DHA, and therefore require these compounds (humans convert about 4% of ALA to DHA and about 6% to EPA and so can utilize plant substances such as flax, soybeans and walnuts in replacement for marine-sources of EPA and DHA) (Gerster 1998). Therefore, using a high-quality supplement that lists the EPA and DHA concentration is important in dogs and cats (many cheaper brands only list total omega-3s, and have low EPA and DHA).

Data supporting using for pain in humans: Recent meta-analysis showed positive results in 10 of 18 qualified RCTs for rheumatoid arthritis (Abdulrazaq 2017). Data less strong for non-immune mediated OA.

Data Supporting Using for Pain in Dogs

RCT with biological markers (Mehler 2016)! Also a variety of studies showing efficacy for dermatologic conditions.

- Drug Interactions and Toxicity

Fat restriction or obesity (debate ongoing re: use in inflammatory bowel conditions and pancreatitis due to anti-inflammatory potential, yet provision of lipids can be detrimental). Decreased platelet aggregation is also reported, and occasional mild gastro-intestinal signs (vomiting, diarrhea). ALA has been reported to have toxicity in dogs at ~200 mg/kg, and in cats at 60 mg/kg (hepatic damage).

- Dosing is recommended to be 50–100 mg/kg of the sum of EPA and DHA, daily, with a maximum dose around 200 mg/kg. If a high EPA and DHA food is fed (geriatric and OA diets, for instance), care should be taken to minimize loss of oils (they are volatile, so food must be stored in air-tight containers), in which case, less supplementation is necessary. Fatty acids are lipids, so care should be taken to reduce calories when these supplements are added, as the inflammation created by obesity is directly contrary to the purpose of fatty acid supplementation.

Avocado-Soy Unsaponifiables (ASU)

Avocado/soybean unsaponifiables are extracts made from avocado and soybean oils, consisting of the leftover fraction (approximately 1%) that cannot be made into soap. ASU is a complex mixture of many compounds including fat-soluble vitamins, sterols (phytosterols β-sitosterol, campesterol, and stigmasterol), triterpene alcohols, etc. The active component(s) remain unknown, but the sterol contents may be the primary contributors to biological activity in chondrocytes (Christiansen 2015). Biological activity has primarily been tested *in vitro*, and is suggested to include: chondroprotective, anabolic (collagen, bone cartilage), and anticatabolic (inhibiting fibrinolysis) properties. It inhibits the breakdown of cartilage and promotes cartilage repair by inhibition of inducible nitric oxide synthase and MMP-13, which are important in OA.

Data supporting use in humans is fair, with a Cochrane review showing that there is moderate-quality evidence that avocado-soybean unsaponifiables (ASU) improved pain and function slightly in the short-term, but may not preserve joint space (Singh 2015). Good evidence has been cited for use of these in human studies of OA (Singh 2015). Data in horses was not significant, and despite *in vitro* improvements in dog studies, there are not RCTs to support or dispute the use of ASUs in pets. (Dasuquin includes ASU with G/C, but data supporting use is *in vitro*).

Green-Lipped Mussels (GLM)

Perna canaliculus

Like glucosamines, GLM are sealife derived, and thought to be anti-inflammatory and chondro-protective. Part of their effect may be related to the PUFAs, as GLMs contain a unique omega-3 FA, eicosatetraenoic acid (ETA), that appears to inhibit both cyclo-oxygenase and lipoxygenase activity *in vitro* (Vandeweerd 2012). There are several studies evaluating increases in omega-3 fatty acids and measures of chronic pain mitigation in dogs, and one in cats. Although some positive results have been achieved, in most of these studies the overall finding is that the placebo groups improved similarly to the GLM groups (aka: huge placebo effect of participating in a dietary study), although in one case, the peak-vertical force measurements were improved in the GLM group (but not the other measures of OA pain) (Rialland 2013). Overall, GLM success in studies has been weak in veterinary species, and in this case, even less studied for OA in people (Cobb 2006). However, with regard to acute muscle damage, there is some evidence supporting anti-inflammatory effects (Mickleborough 2015) and a limited evidence for use in OA in humans (Cobb 2006).

Dose

Green-lipped mussel 30-100 mg/kg (Shmalberg 2014).

Myristol (Cetyl Myristoleate)

Esterified fatty acid supplement from beef tallow is thought to act by suppressing cyclo-oxygenase **and** lipoxygenase pathways, thus suppressing inflammation and prostaglandins. Most data for this product is in rodents. However, two RCTs in humans have shown efficacy for improving knee arthritis symptoms, so weak evidence in favor of this product exists (Lee 2017).

Dose in dogs is 5–10 mg/kg/day, and comes in a product that is combined with various vitamins, MSM and collagen.

Plants (Phytochemicals)

Boswellia serrata

Centuries-old herbal therapy, perhaps better recognized by the resin (Frankincense). *In vitro* studies show decrease in inflammatory mediators (MMP-3, 9 and 13; NO; PGE2), thereby providing chondroprotection. *Boswellia* also shows systemic anti-inflammatory and immunomodulatory effects and cancer-fighting effects, so it's use is more robust than the specifically OA compounds. Rodent models show a decrease in chemical mediators of arthritis, although several of these studies used a combination of herbals (Dragos 2017). Hundreds of studies in rodent models showing various effects on immune and inflammatory markers, effects on OA, cancer, and immune-mediated disease can be found with a simple PubMed search.

Data for Use in Humans

In a recent review, it is stated that "there is high-quality evidence that in people with osteoarthritis *Boswellia serrata* slightly improved pain and function. Further research is unlikely to change the estimates" (Singh 2015). It also has satisfactory data for ulcerative colitis. *Boswellia* absorption is much higher when taken with a fatty meal.

Dose

25–50 mg/kg TID.

Products

Dasuquin advanced has curcumin and *Boswellia* in addition to ASU and G/C. Synovi-G4 has: antioxidants, G/C, MSM, curcumin and *Boswellia serrata*. Platinum performance *Boswellia*.

Drug Interactions and Toxicity

Boswellia is a potent inhibitor of P450 enzyme system in humans; caution when using with other drugs.

Curcumin (Turmeric)

Also a centuries-old herbal therapy, and a commonly used spice in cooking. Powerful anti-inflammatory ability: enough to prevent destructive changes in joints by suppression of NF-kB (similar to betamethasone-steroid) (Dragos 2017). *In vitro* research shows inhibition of all stages of abnormal cell cycle in tumors (Shmalberg 2014).

Data in Humans

Combined with *Boswellia*, objective and subjective improvement for OA that was superior to potent NSAIDs (Dragos 2017). Curcumin has also been shown to be an effective anti-oxidant, and inhibitor of glial activation (thus reducing spinal wind-up).

In dogs, curcumin has poor bioavailability orally. May be most useful for GI inflammatory or neoplastic conditions (Shmalberg 2014). Liposomally encapsulated formulations are being investigated, and may improve the absorption characteristics.

Curcumin

5–50 mg/kg.

Products

Dasuquin Advanced, Synovi-G4, Curcuvet, Platinum Performance.

Arnica montana

Traditionally used for trauma/strain or inflammatory conditions (locomotor, especially). Popularized as a topical application as Traumeel (now T-Relief). A combination of phenols and flavonoids are thought to be the active compounds. Also common as a homeopathic, but this is unlikely to cause any direct effect or toxicity, as the amount of arnica in these compounds is negligible.

"Data for topical use in human knee arthritis and hand arthritis (comparable to ibuprofen), but oral administration is discouraged due to common allergic reactions, inhibition of coagulation, and possible organ damage. Data in animal models: Orally administered, it was shown to alleviate both the histological and radiological changes in the affected joints, in parallel with a decrease in NO, TNF-α, IL-1β, IL-6, and IL-12 concentrations, anti-type II collagen antibodies level, and an improvement of the oxidative status" (Dragos 2017).

Quercitin, Resveratrol, and other Polyphenols (Polyphenols Include Quercetin, Curcumin, Resveratrol - from Grapes, and Oleocanthal)

These compounds, available as supplements but also present in many fruits and vegetables (ginger, curcumin, grapes - skin/seeds, strawberries), generally work through the pathway of anti-oxidation and free-radical scavenging. This can be protective for many degenerative and inflammatory conditions, including OA. Grape seed extract likely derives anti-oxidant properties from the same pathways (Islam 2016). Several are also associated with an anti-cancer effect. A caution with grape-seed extracts is that the safety of these has not been extensively studied in dogs, and renal toxicity remains a concern (especially as the active compound causing grape and raisin toxicity has not yet been established). Resveratrol, a component of wine and grape skins, has a lot of hype on the human side. Although made from grapes, it has not shown toxicity in a rodent and dog model (Johnson 2011). ResveraFLEX is a VetriScience product; it is micro-encapsulated in lipid to allow it to cross cell membranes. The suggested dose of this product is about 5 mg/kg resveratrol daily.

Marijuana and Cannabinoids

Marijuana contains up to 70 cannabinoids (binding CB receptors), up to 140 terpenoids (having serotonergic and anxiolytic effects), and up to 23 flavonoids (having benzodiazepine effects). The two major cannabinoids are delta-9-tetrahydrocannabinol (THC), which is psychoactive, and cannabidiol (CBD), which is not. Endogenous cannabinoids play a homeostatic role in the central nervous system (regulating food intake, dopaminergic reward system, runner's high), pain sensing system and immune system (including microglia).

This is an example of the theoretical advantage of a plant over a synthesized chemical, as it seems that many of these compounds may act synergistically to provide enhanced effect, while also mitigating undesirable side-effects. It is also an example of the complexity of biological based treatments, as the specific compound amounts, quantity, and ratios vary widely between different plants and different growing conditions.

Cannabinoids have been studied for a variety of effects, with pain and epilepsy being the most robust. They modify nociceptive signals peripherally, centrally, and via their glial effects, they are anti-hyperalgesics. They are immunosuppressive and decrease some types of seizures (Booth 2015).

Toxicities

Widely reported in dogs, showing CNS depression (up to death), urinary leakage (direct effect on external urethral sphincter). Cannabinoids are also potent inhibitors of cytochrome P450; use caution in combining with other drugs. **No studies available to guide dosing, or CBD/THC ratios in dogs.**

Vitamins

Vitamins (Ameye 2006) have antioxidant properties (Bujalska-Zadrony 2017), which can help reduce reactive oxygen species in arthritis and other inflammatory conditions. The effects of vitamins C, E, and B on OA have been formally investigated in RCTs, which show variable efficacy. Efficacy and safety studies were not found for dogs and cats. However, these are very popular, and many of these are therefore found in combination products:

- Vitamin C (ascorbic acid) plays a variety of roles in cartilage strength and structure, and has weak data for efficacy in OA in people.
- Vitamin E (various tocopherols) have been mostly disappointing in RCTs in humans.
- Vitamin B (niacinamide) has not shown efficacy for reducing pain in humans.
- Magnesium has been shown to reduce opioid consumption, and has relatively solid data for augmenting analgesia.

Animal Products

Acetyl L-Carnitine

An amino acid that acts as a donor of acetyl groups, helping transfer fatty acids into the mitochondria for oxidative metabolism. It reduces neuro-inflammation, improves nerve recovery, provides analgesia in painful neuropathies, and improves muscle function. ALC has antioxidant and anti-apoptotic activity, exhibits positive effects on mitochondrial metabolism, and shows promise in the treatment of aging and neurodegenerative pathologies by slowing the progression of mental deterioration. In addition, ALC has neuromodulatory effects on both synaptic morphology and synaptic transmission. These effects are likely due to actions of ALC through modulation of gene expression on several targets in the central nervous system (Triana 2016).

Recommended Dose

Acetyl-L-carnitine 50–200 mg/kg/day.

Microlactin

An extract of milk protein derived from hyperimmunized cows (also referred to as hyperimmune milk) which has a large quantity of low and high weight bioactive peptides. IgG type 1 antibodies are prevalent in the high-weight group (compared to regular milk), and the low-weight group appears anti-inflammatory *in vitro*.

Two human RCTs did not show effect, and several studies debunk a correlation between milk products and OA symptoms in people (Singh 2015). One veterinary study suggested an effect using a questionnaire that had not been validated, and did not correlate with DVM exam or any other measure of comfort (not valid, and see comments about placebo effect with nutrition products) (Gingerich 2003). Product available is Duralactin.

Antler Velvet (Elk or Deer)

Reported to provide growth factors to improve physical and sexual performance. Data in humans does not show rigorous testing, and does not merit use (Gilbey 2012). A study in dogs implied a mild effect, but the study design was faulty (Moreau 2004). Furthermore, removal of velvet antler is painful (Woodbury 2002), and the product may be able to cause prion disease (Angers 2009).

This in one of the only compounds discussed today that has obvious reasons to be avoided.

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Veterinary Herbs and Dietary Supplements: Why, What and When?

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Today more than half of Americans use some form of herbal or dietary supplement (HDS). The American Pet Products Association reports that millennials are now the primary pet-owning demographic and many view their pets as family members. Pet owners are interested in more 'natural' health care and treatments for themselves and their pets. One third of dog owners and one fifth of cat owners use supplements. The market for pet supplements reached $580 billion in 2016 and is expected to continue to grow bolstered by a continued focus on health and nutrition in the overall pet market. As it is unknown exactly how many pet owners are using human and/or veterinary herbal or dietary supplements, veterinarians are faced with the challenge of understanding human and veterinary HDS regulation, research, safety, and efficacy.

Regulation of Human Dietary Supplements

Dietary supplements are considered a "food" under the Federal Food, Drug and Cosmetic Act (FFDCA); however, the 1994 Dietary Supplement and Education Health Act (DSHEA) placed supplements in a subcategory with unique guidelines. The DSHEA defines "supplement" as a product taken orally that contains at least one of the following: vitamin, mineral, herbs or other botanicals, amino acids, and substance such as enzymes, organ tissues, glandulars, and metabolites. Dietary supplements can also be extracts or concentrates and are found as tablets, capsules, liquids or powders. Labeling can have claims to affect body function and structure that are not directly related to its nutritional content (www.fda.gov/food/dietarysupplements/ (https://www.fda.gov/food/dietarysupplements/)).

The DSHEA restricted FDA's ability to regulate dietary supplements and premarket safety evaluation is no longer required of new dietary supplements. The HDS manufacturer is responsible for ensuring that their products are safe before marketing. DSHEA provides appropriate labelling statements and requires supplement labels to state, "This supplement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease." DSHEA grants FDA the authority to establish good manufacturing practice (GMP) regulations that govern preparation, packing, and holding of dietary supplements under conditions that ensure their safety. In addition, several independent organizations (U.S. Pharmacopeia, Consumerlab.com (https://www.consumerlab.com/), NSF International) offer quality testing and allow products that pass to display their seals of approval. These seals of approval provide assurance that the product was properly manufactured, contains the ingredients listed on the label, and does not contain harmful levels of contaminants, but do not guarantee that a product is safe or effective. The National Center for Complementary and Integrative Health (https://nccih.nih.gov/about (https://nccih.nih.gov/about)) evaluates scientific research on human herbs and dietary supplements. The NCCIH has adopted the DSHEA supplement definition and refers to these diverse products as 'herbs and dietary supplements (HDS).' Based on NCCIH and DSHEA terms and definitions, pet owners may be giving human HDS, veterinary HDS or both to their pets.

Regulation of Veterinary Herbs and Dietary Supplements

Currently, herbs and dietary supplements marketed for use in non-food producing animals (dog, cat, horses) fall into a 'regulatory gray area.' In 1996, the FDA announced that DSHEA did not apply to animal supplements; therefore, veterinary herbs and dietary supplements have to meet the same regulatory requirements as an animal feed. Currently, products marketed as dietary supplements or "feed supplements" for animals still fall under the Federal Food, Drug, and Cosmetic Act (FFDCA), and the regulations issued under its authority. The Center for Veterinary Medicine (CVM) is responsible for the regulation of animal feed products and has allowed dietary supplements to be marketed, provided that they do not claim to treat, cure, or mitigate disease. The CVM states supplements should conform to the following restrictions:

1. There is a known need for each nutrient ingredient represented to be in the product for each animal for which the product is intended.
2. The label represents the product for use only in supplementation of and not as a substitute for good daily rations.
3. The product provides a meaningful but not excessive amount of each of the nutrients it is represented to contain.

4. The labeling should bear no disease prevention of therapeutic, including growth promotional, representations.

5. The labeling should not be otherwise false or misleading in any particular.

6. The product is neither over-potent nor under-potent nor otherwise formulated so as to pose a hazard to the health of the target animal.

It should be understood that without DSHEA subcategorization, veterinary HDS remain as an unapproved feed supplement or unapproved drug. The FDA does not regulate these products unless they become unsafe or are associated with labels that claim a drug use. Regulation of veterinary products falls to the state and federal officials that are responsible for the implementation of policies that regulate foods, feed additives, and oral animal products. To promote conformity, state and federal feed officials organized the American Association of Feed Control Officials (AAFCO) (www.aafco.org (https://www.aafco.org/)), which develops uniform and equitable laws, standards, definitions, and enforcement policies to regulate the manufacture, labeling, distribution, and sale of animal feeds. AAFCO is a non-regulatory agency that provides these as guidelines which state officials may or may not accept and implement. Historically, AFFCO struggled to establish guidelines for veterinary dietary supplements and the veterinary profession and manufacturers of HDS became proactive forming the National Animal Supplement Council (NASC) (https://nasc.cc/ (https://nasc.cc/)) in 2001. NASC works with the AAFCO and FDA to implement voluntary programs, guidelines, and system for adverse events reporting for veterinary HDS. The NASC is also non-regulatory but offers the NASC Quality Seal program in its efforts "to improve and standardize the industry."

Currently, the American Veterinary Medical Association has a subcommittee considering guidelines and/or policies for the use of veterinary HDS (www.avma.org/News/JAVMANews/Pages/170115a.aspx (https://www.avma.org/News/JAVMANews/Pages/170115a.aspx)) and the American College of Veterinary Nutrition does not have a position on dietary supplements. Furthermore, the AVMA American Board of Veterinary Specialties has received a petition for recognition of the American College of Veterinary Botanical Medicine (ACVBM) as a new recognized veterinary specialty organization. The organizing committee of the proposed ACVBM submitted a letter of intent to the ABVS in 2014 and a formal petition for recognition in 2016 (www.avma.org/News/JAVMANews/Pages/170415b.aspx (https://www.avma.org/News/JAVMANews/Pages/170415b.aspx)).

It should be understood there are no direct federal regulations to ensure safety or efficacy of **either** human or veterinary HDS and veterinarians must understand and recognize human herbs and dietary supplements

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requirements. It is plausible that HDS may provide additional benefits beyond today's complete and balanced pet diets. This is demonstrated in veterinary therapeutic diets (VTD) marketed for disease states which contain specific nutrients or active ingredients that are common herbs or dietary supplements (Table 1).

Table 1. Veterinary therapeutic diets containing herbs and dietary supplements

VTD	Herbs and dietary supplements
Hill's j/m	Omega-3 fatty acids; glucosamine chondroitin; carnitine; antioxidants
RC JS	New Zealand green mussel (GLM); omega-3 fatty acids; glutamine
Purina JM	Omega-3 fatty acids; glucosamine; antioxidant (vitamin A and E)
Hill's Derm Defend	Essential FA; quercetin, bioactives and polyphenols; zinc; vitamin A,E,B complex; beta-carotene
Royal Canin Feline Calm	Hydrolyzed milk protein; L-tryptophan; B vitamins
Hill's c/d Multicare Stress	L-tryptophan; hydrolyzed casein; vitamin E; beta-carotene; omega-3 fatty acids
Purina NeuroCare Canine	Medium-chain triglycerides; antioxidants (vitamin E, C)

Another potential benefit of HDS that is commonly overlooked is utilizing them to increase or decrease circulating drug levels and/or tissue levels. A HDS can be used with drugs to obtain a 'combined effect' that allows for the use of lower drug dosages and decreasing drug side effects. Again we can examine VTD for examples of manipulating HDS-drug interactions to obtain beneficial effects in disease states. For example, Hill's j/d states, "Prescription Diet j/d Canine is clinically tested to reduce NSAID dosage by 25%" and referenced. Alpha lipoic acid, an antioxidant and quercetin, a polyphenol found in Hill's Derm Defend has been shown to inhibit degranulation and histamine release by mast cells. These common supplements could be used synergistically with oral antihistamines. The medium-chain triglycerides (MCT) metabolite caprylic acid reported in Law *et al*. has been shown to dose dependently increase seizure threshold, similar to the antiepileptic drug valproic acid (VPA). VPA also an MCT is the most widely used broad-spectrum antiepileptic in human medicine, but its use is limited by its side effects, such as teratogenicity and hepatotoxicity. It was reported in this study that the MCT diet caused

not only ketone body accumulation but also an increase in MCT in the blood plasma. This suggests synergistic mechanisms might be obtained with MCT supplementation and VPA and/or other antiepileptic drugs.

Evidence-Based Medicine: Herbs and Dietary Supplements

Veterinarians should use evidence-based medicine to determine whether to prescribe an herb or dietary supplement. Evidence-based medicine (EBM) is defined as the integration of best research, clinical expertise, and patient (client) values to make medical decisions in order to improve outcomes. Best research evidence is usually considered randomized, controlled clinical trials (RCCT) or systematic reviews of more than one trial (meta-analysis). Compared to human medicine, RCCT and systematic review/meta-analysis of veterinary standards of care, drugs, and nutrition are not abundant. Furthermore, Toews LC evaluated a sampling of systematic reviews or meta-analyses published in veterinary journals between 2011 and 2015 and concluded most had significant deficiencies that cast doubts on the validity and reliability of reviews based on a potentially biased and incomplete body of literature. It should also be noted that, more often, relevant evidence in veterinary medicine represents the extrapolations of pathophysiological principles, *in vivo* and *in vitro* same and/or other species and logic rather than established facts based on numerous RCCTs or meta-analysis.

As the etiopathogenesis of chronic disease states in companion animals is elucidated, it seems unlikely the model of “one disease, one target, one drug” will provide best treatments and/or management. Similar to human patients, multiple disease states often exist in the canine or feline patient; therefore, treatment shifts to using “multi-drugs” and “multi-targets” models are needed. Systems pharmacology embraces the concept of multiscale systematic modeling of drug/chemical actions by integrating multiple omics data and biological mechanisms. A chemical which can be synthesized (drugs), natural (HDS), or endogenous starts its effects on biological systems through its interactions with biomolecule targets (proteins, DNAs, or RNAs). The change in the functional state of that biomolecule determines the many types of interactions. Multiple targets binding (i.e., polypharmacology) is common with even weak drug or HDS-target interactions having a strong collectively effect on the physiological response. Systems pharmacology fundamentals include developing mechanistic or predictive models through the integration of biological and clinical data and the use of the output from these models for generating new biomedical knowledge.

The primary interest in systems pharmacology is expediting new drug development, but it should be noted that about 80% of antibiotics, cardiovascular, immunosuppressant, and antineoplastic drugs are of plant origin. In fact, about 50% of pharmaceuticals are derived from

compounds first identified or isolated from herbs/plants as active ingredients; therefore, the multidisciplinary research of systems pharmacology can be used to explain the synergism and other mechanisms of drugs and natural products. As the pharmaceutical industry searches for new 'active compounds' with medicinal properties to be synthetically manufactured and patented into profitable drugs, large amounts of *in vitro* or *in vivo* research of herbs and dietary supplements is generated. It has been reported that the success rate of the synthetic route for developing new drugs may be 1/10,000; however, the success rate based on a search of medicinal plants used in various medicine systems can be as high as one in four. For example, there has been a great deal of research in the pharmacology of hemp and marijuana, which both originate from the *Cannabis sativa* plant. From this, we now have the controversial HDS, medical *Cannabis* species and hemp extracts as well as the patented drugs dronabinol (Marinol®) and nabilone (Cesamet™).

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Nutraceuticals - The Good, the Bad and the Evidence Behind Them

38TH ANNUAL OAVT CONFERENCE & TRADE SHOW

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What Is a Nutraceutical?

A food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease.

What Is a Dietary Supplement?

Product taken by mouth that contains a dietary ingredient intended to supplement the diet or a substance produced in purified or extracted form which, when administered orally to patients, aims to provide them the necessary elements for their structure and normal function to better their health and wellbeing.

Nutraceuticals are used by a large number of veterinary clients for osteoarthritis and are one of the fastest growing areas of supplementation for pets.

Normal Joint Structure and Function

The ECM of articular cartilage is mostly protein and water and has both interfibrillar (ground substance) and fibrillar components. The fibrillar component is composed of mostly collagen and elastin. Collagen is the most abundant protein in the body, has a tensile strength similar to steel, is responsible for the integrity of the tissues and their resistance to tensile forces. The interfibrillar component is mostly glycoproteins and proteoglycans (PGs).

Proteoglycans provide the articular cartilage with selective permeability properties and compressive stiffness, while the collagen fibers provide tensile strength.

Proteoglycans have a negative charge & great affinity for water and have the potential to absorb 50 times their weight in water. However, the collagen framework in normal cartilage constrains the proteoglycans and limits their ability to expand to about 20% of their potential. This swelling pressure keeps the cartilage turgid, helping to resist deformation when a compressive load is applied. This dynamic tissue is able to tolerate both compressive and shearing forces without damage, transmitting and distributing the forces to the underlying subchondral bone, which aids in shock absorption.

The proteoglycans in articular cartilage are large aggregates of protein, hyaluronic acid and glycosaminoglycans, predominantly chondroitin 4-sulfate, chondroitin 6-sulfate, and keratan sulfate.

Glycosaminoglycans (GAGs) are long unbranched polysaccharides consisting of a repeating disaccharide unit. This unit consists of an N-acetyl-hexosamine and a hexose or hexuronic acid, either or both of which may be sulfated. The combination of the sulfate group and the carboxylate groups of the uronic acid residues gives them a very high density of negative charge. Members of the glycosaminoglycan family vary in the type of hexosamine, hexose or hexuronic acid unit they contain (e.g., glucuronic acid, iduronic acid, galactose, galactosamine, glucosamine). They also vary in the geometry of the glycosidic linkage (N or O linkage) GAG chains covalently linked to a protein to form proteoglycans.

To review the pathogenesis of osteoarthritis on a cellular level, stresses on the joint lead to production of inflammatory cytokines released by synovial cells, chondrocytes, macrophages and fibroblasts. These proinflammatory cytokines, including certain interleukins and TNF-alpha, lead to upregulation of COX-2 enzymes and production of eicosanoids such as PGE2, and the upregulation of matrix metalloproteinases. Normally during metabolism PGs are broken down by enzymes matrix metalloproteinases (MMPs) and aggrecanase. In acute inflammation MMPs increase in number and disrupt the balance of production and destruction in the joint. There is shift toward breakdown of articular cartilage resulting from an imbalance between MMPs and their TIMP inhibitors, leading to thinning and destruction of the cartilage tissue and perpetuation of the inflammatory cascade with PGE2 production and subsequent pain. On a gross level, the thinning or loss of cartilage leads to joint space narrowing, remodelling of subchondral bone with sclerosis and osteophyte formation, joint effusion, periarticular swelling and pain which may lead to decreased use of the joint and secondary atrophy of musculature.

Goals for a Nutraceutical to Relieve OA Pain

1. Decrease in inflammatory prostaglandin (PGE2)
2. Decrease the production of Pro MMP 2 & 9 and active MMP 2 and 9 (the enzymes responsible for degradation of cartilage
3. Increase the inhibitor of MMP (TIMP-2) to help restore proper balance between these enzymes

Evidence Based Nutraceutical Use

Fish Oil - Omega 3 DHA and EPA[1-4]

Arachidonic acid (AA) is the primary substrate for the lipoxygenase and cyclooxygenase enzymes. This fatty acid is derived from dietary sources and stored in phospholipids of the cell membrane until needed. AA is a member of the omega-6 fatty acid family. AA can be partly replaced in cell membranes by the omega-3 fatty acid eicosapentanoic

acid.

The difference between omega-6 and omega-3 fatty acids centers on the location of the first double bond in the carbon chain, occurring either at the 3rd or 6th carbon from the methyl end. While mammalian cells can elongate and desaturate fatty acids, they are not able to form double-bonds beyond these defining bonds, so are unable to synthesize these fatty acids nor interconvert between these families. Thus, the presence of these fatty acids within cell membranes reflects dietary intake. And this can be important because the physiologic function of the 2 fatty acid families differ.

Eicosanoids are metabolically active compounds derived from 20-carbon fatty acids, usually arachidonic acid. The lipoxygenase (5-LOX) and cyclooxygenase (COX) enzymes are the rate-limiting steps in the production of leukotriene B4, thromboxane A2 and prostaglandin E2. In health, these eicosanoids serve important functions. However, in inflammatory conditions such as arthritis, their production can be increased and their effects can be detrimental. For example, PGE2 can be increased up to 50 fold in arthritic joints. Leukotriene B4 has a potent chemotactic effect and promotes further inflammation. PGE2 and TXA2 both promote the release of tumor necrosis factor alpha and Interleukin 1beta, both which promote further inflammation and, in joints, stimulate the production of matrix metalloproteinases or MMPs. MMPs are the collagen-destroying enzymes that break down articular cartilage in arthritic joints. Further, PGE2 is a potent stimulator of pain receptors, and contributes to the pain of arthritis.

Eicospentaenoic acid (EPA) also can be used by the LOX and COX enzymes to produce eicosanoids. However, when EPA is used by the COX and LOX enzymes, they produce the eicosanoids PGE3, thromboxane (TX) A3 and LTB5, which are less active and relatively antiinflammatory compared to their counterparts produced from AA.

It has been demonstrated that therapeutic diets containing approximately 3.5% omega 3 fatty acids can decrease pain and lameness, improve weight bearing, and decrease the need for NSAIDs in dogs with OA. The primary source of omega 3 fatty acids is fish oil. Approximately 480 mg/kg of fish oil (50–100 mg/kg EPA) would be required as a supplement to match the amounts available in the therapeutic food discussed above. A recent placebo-controlled clinical trial in dogs with OA investigated the effects of a fish oil supplement added to a non-fish based food, dosed at 90 mg/kg EPA and 20 mg/kg DHA. These researchers found significant improvement in indicators of pain and quality of life when comparing the base-line outcome measures to those collected at the end of the 16-week trial. There is a high level of support for supplementation of omega 3 fatty acids.

Mobility Diets

All mobility diets are not created equal! Research shows that 7.5 g EPA + DHA/1000 kcal diet significantly reduced symptoms of arthritis. This amount is quite unwieldy as well as likely to cause diarrhea. Other studies have shown as little as 1 to 3 g/1000 kcal has clinical effect. Ideally for most dogs you would like to get up to the 100 mg/kg of omega 3 for arthritis.

Here is an example:

For a 20kg dog you would like it to receive 2 g of omega 3 total/day for arthritis. This dog would eat around 700 kcal so if feeding a 1.5 g omega 3/1000 kcal diet it would provide approximately 1 gram of omega 3. To make up the additional gram, you would have to supplement with 2 capsules that contain 500 mg of EPA and DHA combined. This is quite feasible.

Green-Lipped Mussel

Perna canaliculus is found in the waters around Australia and New Zealand. It contains EPA, DHA, and ETA. It is also a source of glycoproteins and GAGs. A randomized, double-blind, placebo controlled clinical trial in dogs with chronic pain attributed to OA found significant improvement in mobility and pain in those dogs treated with GLM compared to placebo. The dose used was 50 mg/kg. The antiinflammatory effects of GLM may be derived from its omega-3 fatty acids content or the GAGs or the glycoproteins. This has yet to be determined but it does prove to be at least mildly effective.[6,7]

Avocado/Soybean Unsaponifiables

Avocado soybean unsaponifiables (ASU) are residues of avocado and soy oils combined in a 1:2 ratio to produce a product that has demonstrated anti-arthritic properties. Theoretically, ASU decrease the production of proinflammatory cytokines such as PGE-2 and TNF alpha. In a canine cruciate ligament transection model, ASU administration decreased osteophytes, improved cartilage thickness and produced more normal chondrocytes.[11] Additional *in vitro* studies have shown that the combination of ASU with chondroitin is more effective in decreasing inflammatory cytokines than either product alone. There are no published controlled trials in clinical dogs with OA examining ASU alone or in combination products. However, research on induced arthritis shows a positive result. DASUQUIN (Nutramax) is the product generally used.

Chondroprotectants

Glucosamine/Chondroitin[5]

Glucosamine is a precursor of glycosaminoglycan (GAG). When administered orally, glucosamine is 90% absorbed and undergoes biotransformation in the liver. It is then distributed to tissues and has been shown to have a tropism for articular cartilage. Glucosamine sulfate is absorbed better than glucosamine hydrochloride and may be more effective.

The mechanism of action of glucosamine has not been fully elucidated. *In vitro* studies have shown that when exogenous glucosamine is administered, it is utilized in the synthesis of GAGs. It has also been demonstrated that supplementation with glucosamine inhibits enzymes that are responsible for the degradation of cartilage, and the production of inflammatory mediators is decreased.

Chondroitin sulfate is a much larger molecule than glucosamine, and its oral bioavailability has been questioned. Low-molecular weight chondroitin sulfate is more effectively absorbed by the gastrointestinal tract than larger molecules. Metabolites of chondroitin sulfate are concentrated in articular cartilage. The mechanisms of action of chondroitin are: to stimulate GAG production; inhibit degradative enzymes; enhances the production of hyaluronic acid and prevent the degeneration of type II collagen within articular cartilage. Glucosamine and chondroitin sulfate are often combined in commercially available products. It appears that there is a synergistic effect when the two products are used together.

Studies demonstrating efficacious use of glucosamine/chondroitin are few. McCarthy *et al.* showed glucosamine/chondroitin improved pain, weight bearing and disease severity scores (3/5 measures) but the onset of response was slower for glucosamine/chondroitin compared to NSAIDs.[5] Moreau *et al.* showed no change with the supplement so evidence is conflicting.[12] In a systematic review only 13 studies were controlled and evidence was positive for glucosamine/chondroitin but this is a human study. The level of evidence supporting the use of glucosamine/chondroitin for pain management in dogs is low.

Dosage: Dose at 15 mg/kg on the chondroitin fraction.

Adequan

Not really a nutraceutical but mentioned here.

Polysulfated glycosaminoglycans (PSGAGs) are a semisynthetic product (derived from bovine trachea) structurally similar to the GAGs found in articular hyaline cartilage. PSGAGs stimulate collagen synthesis and inhibit collagen breakdown as well as decrease pain and inflammation. Several studies have documented positive effects when administering PSGAGs (Adequan) to dogs with hip dysplasia and osteoarthritis. One study found decreased hip laxity in dogs treated with Adequan twice weekly from 6 weeks to 8 months of age compared to age-matched controls. It is recommended to begin treatment as early in the disease process as possible in order to slow the progression of cartilage damage. The strength of evidence for PSGAGs used at the labeled dose is considered high. Dose: 5 mg/kg once weekly x 4 to 6 weeks then once monthly in dogs, cats first 4 weeks is the same but 2nd month every other week then once monthly.[10]

Cartrophen

Not strictly a nutraceutical either.

Pentosan polysulphate - this product is used in Canada, Europe and Australia. Similar actions to Adequate. Dose is 1 ml/33 kg once weekly for 4 weeks then once monthly.

Herbals and Natural Supplements

Flex-RX

This product is a bioflavonoid that contains baicalin and catechin and has balanced COX and 5-LOX enzyme inhibition activity. In studies by Burnett *et al.* it showed statistically significant improvement in pain scores when compared to COSEQUIN using veterinarian and owner VAS.

Elk Velvet Antler

Quality elk velvet comes from the antler at the velvet stage and contains chondroitin sulphate, collagen, glycosaminoglycan and pilose antler peptide. Study by Morneau showed improvement in dogs with clinical OA on force plate and by subjective analysis.[12]

Boswellia

This is also known as Indian frankincense in Ayurvedic medicine. Four compounds isolated have been isolated and purified. These have been found to have anti-LOX activity.

This herb is found in human products Flexamine as Aflapin and Osteo-biflex as 5-loxin.

Two placebo controlled clinical trials in humans suggest efficacy for joint pain. In an unblinded open label Austrian study it was found to have 71 percent positive response in clinically lame dogs.[8,9]

Theracurmin

Curcumin is found in veterinary nutraceuticals marketed for arthritis. Its utility as a natural NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells) and cyclooxygenase-2 inhibitor is documented in humans but not in dogs. However, its gastrointestinal absorption in most species appears to be poor. An extract of turmeric, the spice from which curcumin is derived, produced subjective, but not objective, improvements in dogs with arthritis. Theracurmin is a new water soluble curcumin that has shown to have advantages and may have promise in the future in dogs.

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Natural 'Drugs' for Your Pain Management Toolbox

INTERNATIONAL VETERINARY EMERGENCY AND CRITICAL CARE SYMPOSIUM 2017

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Known as supplements, 'nutraceuticals', and phytomedicinals, plant/animal-based therapies are not regulated by the United States Food and Drug Administration (FDA). Thus, unlike pharmaceuticals, manufacturers are not required to provide scientific information to legal authorities for approval. However, supplements are widely used, and many compounds in supplements may be effective. A further complication is in proving the efficacy of supplements; there is the suggestion that it is the interaction of various compounds found in natural substances that generate the clinical effect. This creates a very complicated situation for research, as compared to a single-ingredient pharmaceutical product. Some data is emerging, as companies are motivated by a growing desire for more stringent criteria to produce studies. Unfortunately, many of these continue to be low-quality, without consistent evaluation methods and with varying products/doses, and nearly all with a possible funding bias (paid for by the companies promoting the product) (Bhathal 2017). It is also important to realize the very significant placebo effect attached to non-pharmaceutical interventions, which general further complicates the interpretation of various clinical studies performed to date. In this lecture, we will review the common supplements embraced for pain management (mostly directed at OA), with a balance of possible benefits (often anecdotal or *in vitro*), alongside the presence (or absence) of evidence based medicine (EBM).

Glucosamine/Chondroitin/MSM

Chondroitin is generally produced as chondroitin-sulfate salt. It is intended to inhibit destructive enzymes in joint fluid and cartilage, halt the degradation of cartilage, and with the sulfate, provide essential building blocks for chondrocytes. Glucosamine is sea-life based (lobster, shrimp and crab-shell based) and regulates the synthesis of collagen in cartilage, and may provide mild anti-inflammatory effects. Together, the two nutraceuticals promote the synthesis of glycosaminoglycan and proteoglycan, which are building blocks for the formation of cartilage, protect against synovitis and cartilage degeneration, and modulate metabolism of articular cartilage. *In vitro* results on cartilage are more promising than *in vivo* studies have been, across all species. Some of this may be related to absorption, as glucosamine HCl and chondroitin sulfate require 10 to 20 times the quantity used in *in vitro* studies to reach a plasma concentration that will result in biological activity (Comblain 2016). The glucosamine salt generally used in veterinary products has not been shown to be as well absorbed as the crystalline form, in humans (Bhathal 2017). Many veterinary products are available, and many are combined with other products. This tendency to combine complicates the interpretation of the various studies, as is can be unclear which ingredient mediates the clinical effects (or perhaps, it is the interaction of various ingredients?) MSM is essentially a source of sulfur (duplicate if the chondroitin is bound to sulfur) which is thought to be an important nutrient in cartilage health. MSM has moderate evidence for OA mitigation in humans (Ameye 2006).

Data supporting using it for pain in humans is mixed, but perhaps a bit stronger recently, with a Cochrane meta-analysis showing that most studies are still low-quality but that chondroitin (alone or in combination with glucosamine) was better than placebo (small to moderate effect) in improving pain in participants with osteoarthritis. The conclusion was that the "combination of some efficacy and low risk associated with chondroitin may explain its popularity among patients as an over-the-counter supplement" (Singh 2016). Three review articles summarize data for use in dogs and cats, and none can conclude efficacy or lack of efficacy (Vandeweerd 2012; Bhathal 2017; Comblain 2016). However, the safety of these products has generally outweighed the lack of data, as described in the conclusions of the Cochrane study.

Drug Interactions and Toxicity

Benign - possible mild GI effects, and allergy to ingredients or formulations (glucosamine is sea-food based). Possible concerns with anti-coagulants and anti-hyperglycemics (in humans).

Dosing

Glucosamine ≥25 mg/kg. Chondroitin ≥15–20 mg/kg. MSM >10 mg/kg (Shmalberg 2014).

Hyaluronic Acid (HA)

HA is a high molecular weight glycosaminoglycan that is important in joint fluid, bladder lining, wound healing, etc. In theory, it is the end-product of chondroitin/glucosamine supplementation. It is administered by intra-articular or intra-vesicular (bladder) routes. Oral products are available. In contrast to a 2008 study, HA does not appear to be absorbed orally (Laznicek 2012).

Lipids

Omega Three Fatty Acids

EPA, DHA and ratios. For more detail, see this peer-reviewed, open-access review of ACVN recommendations by Dr. Lenox: http://todaysveterinarypractice.navc.com/role-of-dietary-fatty-acids-in-dogs-cats/ (http://todaysveterinarypractice.navc.com/role-of-dietary-fatty-acids-in-dogs-cats/).

Fatty acids are phospholipids, and are classified as short-chain (<8 carbons), medium chain and long-chain (>12). The presence of double bonds (>2) identify these as poly-unsaturated (PUFA), and the location of the double bonds create the naming (omega-3, 6 or 9). Omega 6 are from animal tissue, sunflower and safflower oils (linoleic acid, arachidonic acid). Omega 3 are from marine and plant sources (Alpha-lipoic acid *ALA, eicosapentaenoic acid *EPA and docosahexaenoic acid *DHA) (Lenox 2016). PUFAs are important mediators of inflammation, with the omega-3s being shown to reduce inflammation is OA, cancer, hyperlipidemia, cardiac, dermatologic, retinal and neurological diseases.

Dogs and cats cannot produce enough omega-3 or omega-6 fatty acids on their own, and require supplementation. Ratios between omega-6:omega-3 supplements have not been found to be important. Omega-6 sources are far more diverse, so supplemental focus falls on the omega-3 fatty acids. Furthermore, unlike humans, dogs and cats do not convert ALA to EPA or DHA, and therefore require these compounds (humans convert about 4% of ALA to DHA and about 6% to EPA and so can utilize plant substances such as flax, soybeans and walnuts in replacement for marine-sources of EPA and DHA) (Gerster 1998). Therefore, using a high-quality supplement that lists the EPA and DHA concentration is important in dogs and cats (many cheaper brands only list total omega-3s, and have low EPA and DHA).

Data supporting using for pain in humans: Recent meta-analysis showed positive results in 10 of 18 qualified RCTs for rheumatoid arthritis (Abdulrazaq 2017). Data less strong for non-immune mediated OA.

Data Supporting Using for Pain in Dogs

RCT with biological markers (Mehler 2016)! Also a variety of studies showing efficacy for dermatologic conditions.

Drug Interactions and Toxicity

Fat restriction or obesity (debate ongoing re: use in inflammatory bowel conditions and pancreatitis due to anti-inflammatory potential, yet provision of lipids can be detrimental). Decreased platelet aggregation is also reported, and occasional mild gastro-intestinal signs (vomiting, diarrhea). ALA has been reported to have toxicity in dogs at ~200 mg/kg, and in cats at 60 mg/kg (hepatic damage).

Dosing is recommended to be 50–100 mg/kg of the sum of EPA and DHA, daily, with a maximum dose around 200 mg/kg. If a high EPA and DHA food is fed (geriatric and OA diets, for instance), care should be taken to minimize loss of oils (they are volatile, so food must be stored in air-tight containers), in which case, less supplementation is necessary. Fatty acids are lipids, so care should be taken to reduce calories when these supplements are added, as the inflammation created by obesity is directly contrary to the purpose of fatty acid supplementation.

Avocado-Soy Unsaponifiables (ASU)

Avocado/soybean unsaponifiables are extracts made from avocado and soybean oils, consisting of the leftover fraction (approximately 1%) that cannot be made into soap. ASU is a complex mixture of many compounds including fat-soluble vitamins, sterols (phytosterols β-sitosterol, campesterol, and stigmasterol), triterpene alcohols, etc. The active component(s) remain unknown, but the sterol contents may be the primary contributors to biological activity in chondrocytes (Christiansen 2015). Biological activity has primarily been tested *in vitro*, and is suggested to include: chondroprotective, anabolic (collagen, bone cartilage), and anticatabolic (inhibiting fibrinolysis) properties. It inhibits the breakdown of cartilage and promotes cartilage repair by inhibition of inducible nitric oxide synthase and MMP-13, which are important in OA.

Data supporting use in humans is fair, with a Cochrane review showing that there is moderate-quality evidence that avocado-soybean unsaponifiables (ASU) improved pain and function slightly in the short-term, but may not preserve joint space (Singh 2015). Good evidence has been cited for use of these in human studies of OA (Singh 2015). Data in horses was not significant, and despite *in vitro* improvements in dog studies, there are not RCTs to support or dispute the use of ASUs in pets. (Dasuquin includes ASU with G/C, but data supporting use is *in vitro*).

Green-Lipped Mussels (GLM)

Perna canaliculus

Like glucosamines, GLM are sealife derived, and thought to be anti-inflammatory and chondro-protective. Part of their effect may be related to the PUFAs, as GLMs contain a unique omega-3 FA, eicosatetraenoic acid (ETA), that appears to inhibit both cyclo-oxygenase and lipoxygenase activity *in vitro* (Vandeweerd 2012). There are several studies evaluating increases in omega-3 fatty acids and measures of chronic pain mitigation in dogs, and one in cats. Although some positive results have been achieved, in most of these studies the overall finding is that the placebo groups improved similarly to the GLM groups (aka: huge placebo effect of participating in a dietary study), although in one case, the peak-vertical force measurements were improved in the GLM group (but not the other measures of OA pain) (Rialland 2013). Overall, GLM success in studies has been weak in veterinary species, and in this case, even less studied for OA in people (Cobb 2006). However, with regard to acute muscle damage, there is some evidence supporting anti-inflammatory effects (Mickleborough 2015) and a limited evidence for use in OA in humans (Cobb 2006).

Dose

Green-lipped mussel 30-100 mg/kg (Shmalberg 2014).

Myristol (Cetyl Myristoleate)

Esterified fatty acid supplement from beef tallow is thought to act by suppressing cyclo-oxygenase **and** lipoxygenase pathways, thus suppressing inflammation and prostaglandins. Most data for this product is in rodents. However, two RCTs in humans have shown efficacy for improving knee arthritis symptoms, so weak evidence in favor of this product exists (Lee 2017).

Dose in dogs is 5–10 mg/kg/day, and comes in a product that is combined with various vitamins, MSM and collagen.

Plants (Phytochemicals)

Boswellia serrata

Centuries-old herbal therapy, perhaps better recognized by the resin (Frankincense). *In vitro* studies show decrease in inflammatory mediators (MMP-3, 9 and 13; NO; PGE2), thereby providing chondroprotection. *Boswellia* also shows systemic anti-inflammatory and immunomodulatory effects and cancer-fighting effects, so it's use is more robust than the specifically OA compounds. Rodent models show a decrease in chemical mediators of arthritis, although several of these studies used a combination of herbals (Dragos 2017). Hundreds of studies in rodent models showing various effects on immune and inflammatory markers, effects on OA, cancer, and immune-mediated disease can be found with a simple PubMed search.

Data for Use in Humans

In a recent review, it is stated that "there is high-quality evidence that in people with osteoarthritis *Boswellia serrata* slightly improved pain and function. Further research is unlikely to change the estimates" (Singh 2015). It also has satisfactory data for ulcerative colitis. *Boswellia* absorption is much higher when taken with a fatty meal.

Dose

25–50 mg/kg TID.

Products

Dasuquin advanced has curcumin and *Boswellia* in addition to ASU and G/C. Synovi-G4 has: antioxidants, G/C, MSM, curcumin and *Boswellia serrata*. Platinum performance *Boswellia*.

Drug Interactions and Toxicity

Boswellia is a potent inhibitor of P450 enzyme system in humans; caution when using with other drugs.

Curcumin (Turmeric)

Also a centuries-old herbal therapy, and a commonly used spice in cooking. Powerful anti-inflammatory ability: enough to prevent destructive changes in joints by suppression of NF-kB (similar to betamethasone-steroid) (Dragos 2017). *In vitro* research shows inhibition of all stages of abnormal cell cycle in tumors (Shmalberg 2014).

Data in Humans

Combined with *Boswellia*, objective and subjective improvement for OA that was superior to potent NSAIDs (Dragos 2017). Curcumin has also been shown to be an effective anti-oxidant, and inhibitor of glial activation (thus reducing spinal wind-up).

In dogs, curcumin has poor bioavailability orally. May be most useful for GI inflammatory or neoplastic conditions (Shmalberg 2014). Liposomally encapsulated formulations are being investigated, and may improve the absorption characteristics.

Curcumin

5–50 mg/kg.

Products

Dasuquin Advanced, Synovi-G4, Curcuvet, Platinum Performance.

Arnica montana

Traditionally used for trauma/strain or inflammatory conditions (locomotor, especially). Popularized as a topical application as Traumeel (now T-Relief). A combination of phenols and flavonoids are thought to be the active compounds. Also common as a homeopathic, but this is unlikely to cause any direct effect or toxicity, as the amount of arnica in these compounds is negligible.

"Data for topical use in human knee arthritis and hand arthritis (comparable to ibuprofen), but oral administration is discouraged due to common allergic reactions, inhibition of coagulation, and possible organ damage. Data in animal models: Orally administered, it was shown to alleviate both the histological and radiological changes in the affected joints, in parallel with a decrease in NO, TNF-α, IL-1β, IL-6, and IL-12 concentrations, anti-type II collagen antibodies level, and an improvement of the oxidative status" (Dragos 2017).

Quercitin, Resveratrol, and other Polyphenols (Polyphenols Include Quercetin, Curcumin, Resveratrol - from Grapes, and Oleocanthal)

These compounds, available as supplements but also present in many fruits and vegetables (ginger, curcumin, grapes - skin/seeds, strawberries), generally work through the pathway of anti-oxidation and free-radical scavenging. This can be protective for many degenerative and inflammatory conditions, including OA. Grape seed extract likely derives anti-oxidant properties from the same pathways (Islam 2016). Several are also associated with an anti-cancer effect. A caution with grape-seed extracts is that the safety of these has not been extensively studied in dogs, and renal toxicity remains a concern (especially as the active compound causing grape and raisin toxicity has not yet been established). Resveratrol, a component of wine and grape skins, has a lot of hype on the human side. Although made from grapes, it has not shown toxicity in a rodent and dog model (Johnson 2011). ResveraFLEX is a VetriScience product; it is micro-encapsulated in lipid to allow it to cross cell membranes. The suggested dose of this product is about 5 mg/kg resveratrol daily.

Marijuana and Cannabinoids

Marijuana contains up to 70 cannabinoids (binding CB receptors), up to 140 terpenoids (having serotonergic and anxiolytic effects), and up to 23 flavonoids (having benzodiazepine effects). The two major cannabinoids are delta-9-tetrahydrocannabinol (THC), which is psychoactive, and cannabidiol (CBD), which is not. Endogenous cannabinoids play a homeostatic role in the central nervous system (regulating food intake, dopaminergic reward system, runner's high), pain sensing system and immune system (including microglia).

This is an example of the theoretical advantage of a plant over a synthesized chemical, as it seems that many of these compounds may act synergistically to provide enhanced effect, while also mitigating undesirable side-effects. It is also an example of the complexity of biological based treatments, as the specific compound amounts, quantity, and ratios vary widely between different plants and different growing conditions.

Cannabinoids have been studied for a variety of effects, with pain and epilepsy being the most robust. They modify nociceptive signals peripherally, centrally, and via their glial effects, they are anti-hyperalgesics. They are immunosuppressive and decrease some types of seizures (Booth 2015).

Toxicities

Widely reported in dogs, showing CNS depression (up to death), urinary leakage (direct effect on external urethral sphincter). Cannabinoids are also potent inhibitors of cytochrome P450; use caution in combining with other drugs. **No studies available to guide dosing, or CBD/THC ratios in dogs**.

Vitamins

Vitamins (Ameye 2006) have antioxidant properties (Bujalska-Zadrony 2017), which can help reduce reactive oxygen species in arthritis and other inflammatory conditions. The effects of vitamins C, E, and B on OA have been formally investigated in RCTs, which show variable efficacy. Efficacy and safety studies were not found for dogs and cats. However, these are very popular, and many of these are therefore found in combination products:

- Vitamin C (ascorbic acid) plays a variety of roles in cartilage strength and structure, and has weak data for efficacy in OA in people.
- Vitamin E (various tocopherols) have been mostly disappointing in RCTs in humans.
- Vitamin B (niacinamide) has not shown efficacy for reducing pain in humans.
- Magnesium has been shown to reduce opioid consumption, and has relatively solid data for augmenting analgesia.

Animal Products

Acetyl L-Carnitine

An amino acid that acts as a donor of acetyl groups, helping transfer fatty acids into the mitochondria for oxidative metabolism. It reduces neuro-inflammation, improves nerve recovery, provides analgesia in painful neuropathies, and improves muscle function. ALC has antioxidant and anti-apoptotic activity, exhibits positive effects on mitochondrial metabolism, and shows promise in the treatment of aging and neurodegenerative pathologies by slowing the progression of mental deterioration. In addition, ALC has neuromodulatory effects on both synaptic morphology and synaptic transmission. These effects are likely due to actions of ALC through modulation of gene expression on several targets in the central nervous system (Triana 2016).

Recommended Dose

Acetyl-L-carnitine 50–200 mg/kg/day.

Microlactin

An extract of milk protein derived from hyperimmunized cows (also referred to as hyperimmune milk) which has a large quantity of low and high weight bioactive peptides. IgG type 1 antibodies are prevalent in the high-weight group (compared to regular milk), and the low-weight group appears anti-inflammatory *in vitro*.

Two human RCTs did not show effect, and several studies debunk a correlation between milk products and OA symptoms in people (Singh 2015). One veterinary study suggested an effect using a questionnaire that had not been validated, and did not correlate with DVM exam or any other measure of comfort (not valid, and see comments about placebo effect with nutrition products) (Gingerich 2003). Product available is Duralactin.

Antler Velvet (Elk or Deer)

Reported to provide growth factors to improve physical and sexual performance. Data in humans does not show rigorous testing, and does not merit use (Gilbey 2012). A study in dogs implied a mild effect, but the study design was faulty (Moreau 2004). Furthermore, removal of velvet antler is painful (Woodbury 2002), and the product may be able to cause prion disease (Angers 2009).

This in one of the only compounds discussed today that has obvious reasons to be avoided.

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Evidence for Use of Nutraceuticals in Osteoarthritis

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Introduction

Nutritional and dietary supplements are often termed nutraceuticals as an amalgamation of the terms nutritional and pharmaceutical. Nutraceuticals still fall into a grey area from a regulatory point of view, yet in recent times has grown into a billion-dollar industry. These products have come a long way since entering companion animal medicine in the early 1990s. The enormous public interest in the relationship of diet supplements and OA often takes center stage when discussing OA and potential therapeutic plans with clients. Unfortunately, speculative information on nutritional based therapies to treat OA has permeated every form of media. The paucity of well-designed scientific studies exploring these treatments leaves clinicians at a distinct disadvantage when discussing possible therapies with clients and colleagues alike. This discussion will focus on the use of evidence based medicine (EBM) when evaluating nutraceuticals. Evidence is defined as "the data on which a judgment or conclusion may be based, or by which proof or probability may be established."[1] The pragmatic use of EBM involves the integration of the best research evidence, clinical expertise and client/patient considerations. There are many ways by which to analyze and integrate evidence into the practice of veterinary medicine, and several schemes by which to rank the strength of evidence. This presentation will be based upon the Food and Drug Administration's (FDA) evidence-based ranking system for scientific data adapted and utilized for study rating and ranking.[2-4] Additionally we will include data which is based upon a modification of this system.[5] Briefly, three separate ratings are used for study evaluation: 1) a rating for study design, 2) a rating for study quality, and 3) a group agent rating for the strength of the entire body of evidence. A final rank of the scientific evidence is decided based upon the classifications from the three rating systems. This system does not use the terms rate and rank interchangeably. These notes will use data directly from two previous publications.[2,4,5] **Certainly everyone can use different criteria to assemble their data and this is only one example methodology and subsequent outcome. This presentation should be not considered a complete resource for all the data available to evaluate nutraceuticals, but instead an example of how to evaluate some of the products currently available.**

Omega-3 Based Diets

Six trials were identified describing the use of omega-3 based diets as the major component for improving the clinical signs associated with osteoarthritis (OA) in dogs.[6-11] All the studies were prospective, randomized, and receive a Type I classification. Examination of the quality of the studies showed that they had adequately addressed issues of scientific quality relating to data collection, analysis, bias, and generalizability. The studies were consistent in finding positive effects of the diets on the clinical signs associated with OA. The studies did vary in outcome measures and this created some differences in ability to assess overall strength but an overall rating of the strength of the evidence concludes that one can have a **high level of comfort** with the results of the aforementioned studies. Given the consistency of the findings, one can also have confidence in the data that shows that these diets are effective (Appendix 1).

Compounds Based Upon Chondroitin Sulfate, and Glucosamine Hydrochloride

Two trials were identified describing the use of compounds with chondroitin sulfate, and glucosamine hydrochloride as major components for improving clinical signs associated with OA in dogs.[12,13] Both study designs were prospective, randomized, and receive a Type I classification. One study subjectively showed a positive effect,[13] while the other showed no positive effect[12]. Examination of the quality of the studies showed that they had adequately addressed issues of scientific quality relating to data collection, analysis, bias, and generalizability. There was a low consistency rating meaning the results were inconsistent between the studies. The studies do provide information to conclude that there was some suggestion that the effect will be physiologically meaningful and achievable. An overall rating of the strength of the evidence concludes that one can have a moderate level of comfort with the results of the aforementioned studies. However, confusion arises in which study do you use to help make your decision on whether or not to use this type of product.

Green-Lipped Mussel Preparation

Three trials were identified using a compound that's main ingredient was green-lipped mussel (*Perna canaliculus*) for the treatment of OA in dogs.[14-16] The studies were prospective, randomized in design and received a Type I rating. While the studies subjectively showed a positive effect, the studies get a quality rating that suggests some uncertainties exist relating to the scientific quality. There was a moderate level of consistency between the studies. The studies do provide information to conclude that there was some suggestion that the effect will be physiologically meaningful and achievable.

An overall rating of the strength of the evidence concludes that one can have a moderate level of comfort with the results of the aforementioned studies.

Zeel® Homeopathic Preparation

Two trials were identified using Zeel® for the treatment of OA in dogs. While both were prospective, only one was randomized and blinded. Both studies showed subjective positive effects of the product, however, in one study, the effects were less than those produced by carprofen. Again, given the small sample sizes and the study limitations there are some uncertainties relating to the scientific quality. An overall rating of the strength of the evidence concludes that one can have a low to moderate level of comfort with the results of the aforementioned studies and the positive effects seen with these compounds.

Elk Velvet Preparation

Velvet from elk antlers was tested as an additive to the food of OA dogs. One randomized, blinded, placebo-controlled, parallel group clinical trial as a treatment for osteoarthritis was evaluated.[17] This study is classified as type I study. The study had positive efficacy data from objective and subjective outcome measures. Examination of the quality of the studies showed that it had adequately addressed issues of scientific quality relating to data collection, analysis, bias, and generalizability. The study does provide information to conclude that there was some suggestion that the effect will be physiologically meaningful and achievable. An overall rating of the strength of the evidence concludes that one can have a moderate level of comfort with the results of the aforementioned study.

Brachystemma calycinum D. Don

Brachystemma calycinum D. Don was tested in one randomized, blinded, placebo-controlled, parallel group clinical trial as a treatment for osteoarthritis was evaluated.[18] This study is classified as type I study. The study had positive efficacy data from objective and subjective outcome measures. Examination of the quality of the studies showed that it had adequately addressed issues of scientific quality relating to data collection, analysis, bias, and generalizability. The study does provide information to conclude that there was some suggestion that the effect will be physiologically meaningful and achievable. An overall rating of the strength of the evidence concludes that one can have a moderate level of comfort with the results of the aforementioned study.

S-Adenosyl L-Methionine

S-adenosyl l-methionine (SAMe) was evaluated in one randomized, blinded, placebo-controlled, parallel group clinical trial as a treatment for canine osteoarthritis.[19] This study is classified as type I study. The study had consistent data from objective and subjective outcome measures showing no positive effect. Examination of the quality of the studies showed that it had adequately addressed issues of scientific quality relating to data collection, analysis, bias, and generalizability. The study does provide information to conclude that there was some suggestion that the effect will be physiologically meaningful and achievable. An overall rating of the strength of the evidence concludes that one can have a moderate level of comfort with the results of the aforementioned study.

P54FP

P54FP is an extract of *Curcuma domestica* and *Curcuma xanthorrhiza*. One randomized, blinded, placebo-controlled, parallel group clinical trial of P54FP as a treatment for osteoarthritis of the canine elbow or hip was evaluated.[20] This study is classified as type I study. The study had conflicting data from objective and subjective outcome measures. Examination of the quality of the studies showed that it had adequately addressed issues of scientific quality relating to data collection, analysis, bias, and generalizability. The study does provide information to conclude that there was some suggestion that the effect will be physiologically meaningful and achievable. An overall rating of the strength of the evidence concludes that one can have a low level of comfort with the results of the aforementioned study.

Resin Extract of *Boswellia serrata*

One trial with an herbal dietary supplement consisting of a natural resin extract of *Boswellia serrata* was conducted to evaluated effects on OA in dogs.[10] The study is classified with a Type III rating.[2] Subjective clinical improvements identified. As for a quality rating, the study did not adequately addressing the important issues of scientific quality as defined by Aragon 2007. An overall rating of the strength of the evidence concludes that one can have a low level of comfort with the results of the aforementioned study.

It is important to note that this type of evaluation system does not rate the products or studies.

What it does do is provide the reader with a sense of the reliability of the data presented to them and how comfortable they can be with the results that they are presented in each study. Furthermore, systematic reviews rarely consider the safety of any therapies and focus solely on efficacy. Weakness of systematic reviews will be discussed.

Appendix 1: Strength of Evidence Ranking

A "high level of comfort" ranking advises that qualified scientists agree that a specific claim is scientifically valid. This highest level of ranking possesses a very low level of probability that new scientific data will overturn the conclusion that the relationship in question is valid or significant. This rank is based on relevant, high quality studies of study design Types I and II with sufficient numbers of individuals resulting in a high degree of confidence that the results are relevant to the target population.

A "moderate level of comfort" ranking describes a relationship as promising but not definitive. The claim is based on relevant, high to moderate quality studies of study design Type III and higher and sufficient numbers resulting in a moderate degree of confidence that the results could be extrapolated to the target population.

A "low level of comfort" ranking possesses a low consistency. The relationship is based on moderate to low quality studies of study design Type III and has insufficient numbers of individuals tested resulting in a low degree of confidence that the results could be extrapolated. Uncertainties would also exist as to whether the proposed benefit(s) would be physiologically meaningful and achievable.

An "extremely low level of comfort" ranking has very low consistency and is based on moderate to low quality studies of design Type III and insufficient numbers resulting in a very low degree of confidence that the results could be extrapolated.

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Speaker Information

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Weight loss, when indicated, will ameliorate clinical signs of OA due to decreased forces being placed on joint surfaces. In fact, weight loss may help reduce the dose or frequency of symptomatic therapy using nonsteroidal antiinflammatory drugs (NSAIDs). Weight reduction prior to surgery will reduce postoperative stress placed on the surgical repair, but is not mandatory. Oftentimes, exercise is difficult until a predisposing cause of osteoarthritis is eliminated. Enforced rest and restricted activity provide an opportunity for transient episodes of inflammation to resolve, in addition to decreasing stress placed on surgical repair. Controlled moderate exercise should be instituted long term to help avoid loss of range of motion due to joint capsule fibrosis, to maintain or build muscle mass, and to promote the physiologic health of articular cartilage and improve body condition scores.

Pharmacological management of OA is important for three reasons - to decrease inflammation, to provide analgesia, and to improve function. Consideration should be given to drugs that inhibit the release or activity of prostaglandins, leukotrienes, neutral metalloproteases (stromelysin, collagenase), serine proteases, oncoproteins, interleukins, and tumor necrosis factor. Nonsteroidal antiinflammatory drugs and glucocorticoid drugs are common examples. Other products, such as the slow-acting disease-modifying osteoarthritic agents (SDMOA), are purported to only inhibit mediators of inflammation within the joint, but also may stimulate metabolic activity of synoviocytes and chondrocytes. These products are available in injectable and oral forms.

Goals for Treatment of Surgical Pain

The best strategy for treating surgical pain is avoiding pain. Preemptive analgesia is a must, not only to reduce pain, but also to lower the amount of anesthetic delivered to the patient. Surgical trauma should be minimized by use of meticulous operative technique, use of minimally invasive procedures, and use of arthroscopy. Surgical time should be kept to a minimum, as prolonged times significantly increase the chance of infection and the associated pain. Postoperative pain management should be a complement to your preoperative plan. The amount of postoperative analgesia required is inversely proportional to the effectiveness of preemptive analgesia.

Preemptive analgesia - Analgesic agents should be administered to patients prior to the onset of noxious stimuli to decrease the intensity and duration of pain. Less analgesic drug is needed to keep an animal comfortable if given before a painful stimulus occurs. Typically, preemptive analgesia is administered shortly before anesthetic induction occurs (30–90 minutes prior to induction). Preemptive analgesia can include anesthetic premedications such as opioids, alpha-2 agonists, and nonsteroidal antiinflammatory drugs. Local anesthetic techniques including epidural anesthesia, intraarticular anesthesia, and local nerve blocks are also very useful. Opioids and bupivacaine are good agents for epidural administration. Bupivacaine is also ideal for local and intraarticular blocks.

Postoperative analgesia - Preemptive analgesics may need to be "topped off" following surgery. Premature "topping off" can dramatically delay endotracheal tube removal; therefore, I prefer to administer postoperative medications once a gag reflex has returned and the endotracheal tube is removed. Other non-drug treatments for postoperative pain include bandaging and cold therapy. Animals are much more comfortable if mild external pressure is applied to a wound. Mild external pressure prevents excessive swelling and accumulation of fluid in dead space - both of which cause stretching of tissues and triggering of pain receptors. Cold therapy also reduces swelling but also causes local numbing, helping to reduce the sensation of pain.

Analgesic Drugs

1. Nonsteroidal Antiinflammatory Drugs

Nonsteroidal antiinflammatory drugs (NSAIDs) are widely accepted as the gold standard for treatment of OA in dogs and are used as a means of reducing prostaglandin synthesis (primarily PGE_2) through inhibition of cyclooxygenase. There are a variety of NSAID options in dogs and cats. One NSAID may provide superior results to another in certain pets. The common NSAIDs used in dogs for treatment of OA include carprofen, deracoxib, meloxicam, and firocoxib. There is not an approved NSAID for chronic treatment of cats with OA. NSAIDs approved for short-term relief of surgical pain in cats include meloxicam and robenacoxib.

Carprofen

Carprofen (Rimadyl) is a NSAID product from Zoetis Animal Health, is approved for treatment of pain and inflammation associated with osteoarthritis and for the control of postoperative pain associated with soft tissue and orthopedic surgeries in dogs. Carprofen is available for oral use in caplet and chewable tablet formulations in 25-mg, 75-mg, and 100-mg sizes. Injectable carprofen became available in 2003, and its use for preemptive analgesia and rapid pain control has become common. Carprofen is licensed for subcutaneous use, but extralabel intravenous administration is commonly performed.

Carprofen is routinely used for preemptive and postoperative analgesia. When used for control of surgical pain, the first dose of carprofen can be administered approximately two hours prior to the procedure and then continued postoperatively according to the needs of the individual case. The recommended dose is 4.0 mg/kg. If used preemptively, the drug can be administered at the time of premedication or induction of anesthesia. The effect on bleeding at surgery does not appear to be a clinical problem. A short-lived mild inhibition has been seen experimentally, but bleeding times are normal when evaluated in clinical patients. Coagulation tests including PT, APTT, and ACT are also normal following injectable carprofen.

Gastroduodenal protection occurs due to carprofen's enhanced cyclooxygenase-2 (COX-2) activity. The majority of NSAIDs in the past have primarily been cyclooxygenase-1 (COX-1) inhibitors, which leads to widespread PGE_2 inhibition including that found in the gastrointestinal tract, joints, and kidneys. COX-2 inhibitors have their predominant effect on cyclooxygenase in the joint. Carprofen is given at a dose of 2.2 mg/kg PO every 12 hours, or 4.4 mg/kg PO every 24 hours. The flexibility of giving Rimadyl either once or twice a day is an added advantage, allowing owners to choose the best option to fit their schedule. Plasma and serum concentrations of carprofen are

consistent throughout the treatment period. Serum concentrations peak at 2 hours, while synovial concentrations peak between 3–6 hours. The synovial concentration of carprofen ranges between 1–10 µg/ml during the treatment period in both normal and osteoarthritic joints. A significant reduction of PGE_2 from chondrocytes occurs at all concentrations in this range. An idiosyncratic side effect has been reported in dogs on carprofen; rare dogs were reported to have reversible hepatotoxic effects leading to icterus and elevation of alkaline phosphatase and hepatic transaminases. The incidence of this and other side effects is very low (well less than 1%). Recent studies have shown carprofen to have little effect on kidney and platelet function. Carprofen has been recently found to support cartilage metabolism and proteoglycan synthesis. Carprofen has been anecdotally reported to have success in treatment of osteoarthritic and postoperative pain in cats at a dose of 12.5 mg PO every 5 days. No severe adverse reactions have been reported at this dose. The use of carprofen in cats is extralabel - this drug is not approved for use in cats, and no clinical research data is available to substantiate the anecdotal regimen mentioned above. Cats have been found to be sensitive to the NSAID class of drugs due to differences in liver metabolism of this type of drug.

Deracoxib

Deracoxib (Deramaxx) is a NSAID from Elanco Animal Health, approved for use in dogs. The product is available as a chewable tablet. The recommended dose is 3–4 mg/kg PO once daily for 7 days, or 1–2 mg/kg PO SID for chronic use. Like carprofen, deracoxib has a highly favorable COX-2:COX-1 ratio. The expected side effects are similar to other NSAIDs, primarily gastrointestinal disturbances.

Meloxicam

Meloxicam (Metacam) is a recently released NSAID by Boehringer-Ingelheim (distributed by Merial in the U.S.), approved for treatment of postoperative pain in dogs. An oral and injectable form are available. The oral form is a suspension that can be applied to the pet's food or administered directly into the mouth. The dose for dogs is 0.1 mg/kg PO once daily. A loading dose of 0.2 mg/kg can be given the first day. The oral liquid is calibrated at 1 drop = 1 lb body weight to simplify administration. This is particularly useful for patients having a small body size. The injectable form (5 mg/ml) is administered at 0.2 mg/kg IV or SQ. This is equivalent to giving 1 ml for every 55 lb of body weight for the first dose. If a subsequent dose is given, it should be reduced to half the dose. The oral form can be used after 24 hours at a dose of 0.1 mg/kg once daily.

Firocoxib

Previcox (firocoxib) chewable tablets are indicated for the control of pain and inflammation associated with osteoarthritis and for the control of postoperative pain and inflammation associated with soft-tissue and orthopedic surgery in dogs. Previcox is available as round, beige to tan, half-scored tablets in two strengths, containing 57 mg or 227 mg firocoxib. The approved dose in dogs is 5 mg/kg once daily. Like deracoxib, firocoxib has a highly favorable COX-2:COX-1 ratio. The expected side effects are similar to other NSAIDs, primarily gastrointestinal disturbances.

2. Glucocorticoids

Glucocorticoids have been traditionally used to treat DJD only when other more conventional means of therapy have been ineffective. Glucocorticoids effectively reduce inflammation by inhibiting chemotaxis of neutrophils, decreasing microvasculature permeability, inhibiting cyclooxygenase and thereby decreasing prostaglandin production, inhibiting lipoxygenase and thereby decreasing leukotriene production, inhibition of interleukin-1 release, inhibition of oxygen free-radical generation, inhibition of metalloproteinases, and stabilization of lysosomal membranes. The use of glucocorticoids for treatment of DJD would appear to be ideal due to their generalized inhibition of inflammatory mediators and cytokines; however, chronic use of these drugs has been found to delay healing and initiate damage to articular cartilage. Prednisone is given orally at an initial dose of 1–2 mg/kg once daily in dogs, and 4 mg/kg once daily in cats. The potential systemic side effects of glucocorticoids are well documented; therefore, low-dose (0.5–2.0 mg/kg in dogs and 2.0–4.0 mg/kg in cats), alternate-day therapy is the goal if long-term therapy is instituted. Intraarticular injection of 5-mg triamcinolone hexacetonide in dogs suggested a protective effect not only under prophylactic, but also under therapeutic conditions in an experimental DJD model. The sparing effect on cartilage appeared to be due to decreased production of stromelysin, interleukin-1, and oncoproteins. At best, treatment of DJD with corticosteroids is controversial and should be used for a short period of time.

3. Chondroprotective Agents

Chondroprotective agents are emerging as a new class of drugs used to slow progression of and treat chronic DJD. These drugs not only should be antiinflammatory, but they also should support anabolic (repair) processes in cartilage, bone, and synovium essential for normalization of joint function. This class of drugs includes the glycosaminoglycans. Examples of these drugs include glycosaminoglycan polysulfate ester, pentosan polysulfate, and sodium hyaluronate.

Adequan (Elanco Animal Health) is a glycosaminoglycan polysulfate ester (GAGPS), which is purported to provide chondroprotection due to the inhibition of various destructive enzymes and prostaglandins associated with synovitis and DJD. Chondrostimulatory effects are also purported as a result of increased synoviocyte secretion of hyaluronate and enhanced proteoglycan, hyaluronate, and collagen production by articular chondrocytes. While the majority of experimental and clinical studies support the premise that GAGPS possess properties of chondroprotection and chondrostimulation, some studies have found GAGPS to have either no beneficial effect or to actually have a detrimental effect on cartilage metabolism.

A clinical study in hip dysplastic dogs found the greatest improvement in orthopedic scores at a dose of 4.4 mg/kg (2 mg/lb) given intramuscularly every 3 to 5 days for 8 injections. The improvement in orthopedic score was not statistically significant, however. Another study found twice-weekly intramuscular administration of 5.0 mg/kg GAGPS from 6 weeks to 8 months of age in growing pups that were susceptible to hip dysplasia resulted in less coxofemoral subluxation. The longevity of relief provided by GAGPS is unknown. Most studies have evaluated its effect in the short term only. Anecdotal reports of duration of amelioration of clinical signs range from days to months. It is also not known whether the complete series of injections are needed once clinical signs return or whether a shorter regimen would suffice. The recommended dose for Adequan in dogs and cats is 2 mg/lb IM every 5 days for 8 treatments.

Side effects of GAGPS in dogs include short-term inhibition of the intrinsic coagulation cascade as well as inhibition of platelet aggregation. Also, GAGPS has been found to inhibit neutrophils and complement that may predispose to infections, especially when injected intraarticularly under contaminated conditions.

Sodium hyaluronate has been touted to promote joint lubrication, increase endogenous production of hyaluronate, decrease prostaglandin production, scavenge free radicals, inhibit migration of inflammatory cells, decrease synovial membrane permeability, protect and promote healing of articular cartilage, and reduce joint stiffness and adhesion formation between tendon and tendon sheaths. In the past, sodium hyaluronate has generally been recommended for mild to moderate synovitis and capsulitis, rather than osteoarthritis. Recently, the drug has gained popularity for its use for treatment of osteoarthritis. Sodium hyaluronate is usually administered intraarticularly. Hyaluronate was used in experimental dogs at a dose of 7 mg per joint, intraarticularly, once weekly with success in slowing DJD.

4. Nutraceuticals

These preparations are actually promoted as nutritional supplements rather than pharmaceuticals. These products are also referred to as chondroprotectants by some. Manufacturers have labeled these products as nutraceuticals. Unfortunately, most of these products have little controlled experimental or clinical research in dogs to substantiate their effectiveness; however, several studies are presently underway. In addition, little regulation of these products is available or enforced. Oral glycosaminoglycan, glucosamine, free-radical scavenger and herbal products are currently being marketed. Most glycosaminoglycan compounds contain varying amounts of chondroitin sulfates. Dosages vary between products; therefore, manufacturer recommendations should be followed. These products are used alone or often in combination with NSAIDs. Few side effects have been reported with these products.

Cosequin and Dasuquin (Nutramax Laboratories) are marketed as a glycosaminoglycan enhancer, capable of providing raw materials needed for the synthesis of extracellular matrix of cartilage. Unlike most nutraceuticals, Cosequin has been evaluated in a variety of studies. Cosequin contains glucosamine, which has been described as the building-block of the matrix of articular cartilage. It has been described as a preferential substrate and stimulant of proteoglycan biosynthesis, including hyaluronic acid and chondroitin sulfate. Cosequin also contains chondroitin sulfate, mixed glycosaminoglycans, and manganese ascorbate for the purpose of promoting glycosaminoglycan production. Dasuquin contains similar components with the addition of ASU. Mixed results have been seen in control of pain and clinical signs of OA with these products in man and dogs, but these products are often used in a multimodal approach to management of OA in dogs and cats. No significant side effects have been reported with Cosequin or Dasuquin.

Antinol (Vetz Petz) is a new fatty-acid supplement that is a natural product derived from the New Zealand green-lipped mussel. Antinol features antiinflammatory properties due to the presence of purified fatty acids and has been shown to have no known side effects in dogs and cats. It is commonly used to help control clinical signs and reduce progression of OA in dogs and cats. Antinol can be used in conjunction with NSAIDs without side effects, and a synergistic relationship with the two products has been observed. Antinol appears to work well as a long-term maintenance therapy for osteoarthritis and decreases the chance of side effects seen with prolonged NSAID use. A strategy that has worked well for me is daily Antinol with addition of a NSAID on an as-needed basis.

SPEAKER INFORMATION

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