An Introduction to Supplements: Evidence-Based Nutritional Therapies

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According to the National Research Council (NRC) an *Animal Dietary Supplement* is a substance for oral consumption by horses, dogs, or cats, whether in/on feed or offered separately, intended for specific benefit to the animal by means other than provision of nutrients recognized as essential, or provision of essential nutrients for intended effect on the animal beyond normal nutritional needs, but not including legally defined drugs.[1] The term *Nutraceutical* has no official definition but has been defined as a dietary supplement that is intended for health benefits beyond prevention of essential nutrient deficiencies.

The use of animal dietary supplements is widespread. Surveys show that 10% - 33% of US dogs, cats, and horses receive a daily supplement and 90% of US vets dispense supplements.[1-3] I will limit this presentation to non-herbal, nutritional supplements.

Animal Supplement Oversight

Human and animal supplements are not subject to the same regulations or regulators. At the federal level, animal supplements are regulated by the Food & Drug Administration, Center for Veterinary Medicine (CVM). The CVM may recognize them as either foods or as drugs depending on the intended use of the product as established by the labeling claims. The difference in CVM status is determined by how the supplement company presents the product.[4]

If the animal supplement is bought to the market as a food, there are no registration or pre-market clearance requirements by the CVM, provided the product contains ingredients recognized for the approved nutritional purpose. In this scenario, suspicious ingredients must be brought to the attention of the CVM for approval. At the state level these supplements are usually overseen by the state's agriculture department (often adopting AAFCO standards). Interpretation and enforcement of regulations differs by state. Such a supplement must be registered with the state, or the company licensed in the state, prior to product distribution. This usually involves the submission of labels to the state (every state) or registration of the company.[4]

Alternatively, an animal supplement, for a health purpose, may be labeled similarly to an animal drug. Such supplements are still subject to CVM oversight and also that of states with animal remedy laws. These supplements that cannot meet the FDA drug approval requirements may be allowed to be marketed as "unapproved drugs of low regulatory priority" by the CVM. [The CVM has enforcement discretion to allow marketing of products for which there are reasonable assurances that the company is acting responsibly. This discretionary enforcement may also apply to topical meds, those equivalent to OTC human drugs, and petroleum-containing cat laxatives.] These supplements must conform to CVM labeling requirements. Furthermore, the

company should register as a drug manufacturer with the FDA, "drug list" the product, and follow GMPs.[4]

Given all of this official oversight of supplements you would think that those available must be safe and effective, right? The truth is that the regulations for pet products are not well defined; thus, it is easy for poor quality manufacturers to sell their pet products. Furthermore, the lack of federal and state resources results in ineffective monitoring and control of what is on the market, leaving the impression that supplements are unregulated.

Supplement Security

We all want to be sure to dispense safe and effective therapeutics. Unfortunately, with little regulatory enforcement there is a high potential for ineffective, or even unsafe, supplements making fraudulent claims to be readily available to our clients. When you add to this the recent, vast proliferation of nutritional supplements coupled with their promotion and availability on the internet, the veterinarian is left in a difficult position. How do we choose supplements that we can trust and dispense?

The first thing to do is to evaluate the supplement company. We need to ask such questions as:

1. How long have they been in business? (Generally, the longer the better)
2. What is the company's track record/reputation? (Colleagues/VIN Alt Med message board)
3. Contact the company with questions. (How responsive are they?)
4. Who is involved with formulating the products? (Nutritional experts/veterinarians are best)
5. What kinds of claims are being made? (If unbelievable, don't believe it)
6. Is there specific safety/efficacy research on this product?
7. Is there a guaranteed analysis?
8. Is there a lot # and expiration date?
9. National Animal Supplement Council (NASC) - www.NASC.cc

Prescribing Supplements

The next step in prescribing a supplement is to assess the need for it. This requires an accurate diagnosis of the pet's condition. Then, research on the proposed supplement itself is needed. Looking at research provided by the manufacturer is a place to start. Additionally, a literature search may be helpful. Check out pubmed, google scholar, and National Institutes of Health Office of Dietary Supplements (ODS) - https://ods.od.nih.gov/Research/resourcesforresearchers.sec.aspx

Ultimately, the final step in prescribing a supplement is to assess outcomes. This requires keeping searchable records and periodically evaluating the supplement's effectiveness.

Supplements for Healthy Pets

Commercial Pet Diet Processing - Destroys Nutrients

Cooking (112^{o} F – 117^{o} F) reduces potency of almost all nutrients and completely destroys others including Thiamine, Folic Acid, Vitamin C, Vitamin A, Niacin, and Pantothetic Acid.[5-11] While pet food manufacturers add back nutrients to balance the diets, they proceed based on incomplete knowledge. Even the experts agree that the AAFCO standards are lacking.

According to Dr. David A. Dzanis, "The formulation method does not account for … availability of nutrients. Yet a feeding trial can miss some chronic deficiencies or toxicities."[12] Dr. Quinton Rogers stated, "Although the AAFCO profiles are better than nothing, they provide a false security... Some foods that pass the feeding trials still won't support animals over the long term."[12] Finally, from Dr. Tony Buffington, "The recommendation to feed one food for the life of an animal gives nutritionists more credit than we deserve."[12] Dr. Richard Hill said that it is a myth to think that "The minimum and maximum amount of essential nutrients that should be included in the diet is known for most nutrients in normal dogs and cats."[13]

Besides the 40 or so nutrients that AAFCO recognizes, research shows that there are over 8,000 phytochemicals present in whole (unprocessed) foods and that these nutrients work together synergistically to create health.[14] Furthermore, many of these natural compounds have biological effects that make them equally essential for life as vitamins.[15]

The bottom line is that healthy pets that are eating a "complete and balanced" diet may benefit from nutritional supplements.

Supplements for Sick Pets

No matter what the etiology, disease leads to compromised cells. Damaged cells require increased metabolic activity to remove debris and rebuild cell structures. Up-regulation of metabolic pathways leads to an increased nutrient demand. Without proper nutritional support, healing can be delayed or incomplete. So, every case has a nutritional component and may benefit from nutritional supplements.

Specific Supplements

Whole-Food Multivitamin – As described above, processed pet foods lack the thousands of micro-nutrients found in whole foods. Compounding this is the fact that most pet caregivers feed less food than the label calls for because the high energy-density causes weight gain. (The pet food's nutrient profile is based on the pet getting the prescribed volume of food.) In my opinion, every pet benefits from a whole-food multivitamin.

Probiotics/Prebiotics – Probiotics are supplements that provide the gut with the beneficial bacteria needed for health. Prebiotics are the nutrients the probiotics need to survive in the intestines. Dogs and cats did not evolve eating sterile diets. The freshly killed and not-so-freshly

killed animals they consumed were teaming with bacteria. Is it any wonder that so much research demonstrates the benefits of probiotic supplementation for pets?

There are more bacterial cells in the body than body cells themselves. From a cellular standpoint, we are more bacterial than we are human. The complex internal ecology within the body and the associated genetic fingerprint is called the intestinal microbiome –micro for microscopic and biome for a naturally occurring community of flora occupying a large habitat. We interact with the bacteria and their genes. The gut microbiome may be considered an organ just as vital to health as the liver, heart, or brain.

The beneficial bacteria in the intestine help to further break down foods to liberate the nutrients. They also manufacture several vitamins. Probiotic bacteria competitively inhibit pathogenic bacteria. They nourish the enterocytes with short-chain fatty acids and help to maintain the integrity of the intestinal lining, protecting the entire body from the inflammation caused by leaky gut syndrome.

Furthermore, the Gut Associated Lymphoid Tissue (GALT) makes up 70% - 80% of the immune system. Research shows that the balance of intestinal bacteria affects the systemic immune system. In fact, probiotic supplements have a profound effect on immune function.

In one study,[16] puppies given a probiotic supplement produced higher titers to vaccines. Another study[17] showed that puppies that were given a probiotic supplement before six months of age were less likely to develop immunes system changes associated with atopic dermatitis.

There is also a close link between the intestinal microbiome and the brain. Seventy to eighty percent of the body's serotonin is made by the GI neurons. The intestinal nervous system is considered by some to be the body's second brain. There is bidirectional communication between the intestinal microbiome and the brain via the vagal nerve.

One study[18] showed that chronic administration of probiotics to mice reduced levels of anxiety and depression-like behavior and induced changes in GABAergic system in regions of the brain known to involve these behaviors. Vagotomy prevented the effects of the probiotic.

Omega-Three Fatty Acids – Another nutrient group that is vital for pet health is omega-three fatty acids. The meats used in most pet foods are lower in omega-three fatty acids than the ancestral diet of pets. Most farm animals are fed grains which are high in omega-six fatty acids. This leads to meat high in omega-sixes and low in omega-threes. The wild prey of ancient dogs and cats ate mostly grasses which are high in omega-three fatty acids, which increases the omega-three to omega-six ratio. Omega-six fatty acids are pro-inflammatory while omega-three fatty acids are anti-inflammatory. It is important to balance the body's system toward less inflammation.

Omega-three fatty acids, specifically docosahexaenoic acid (DHA), are also very important in proper neurological development and function. That is not surprising when you consider that DHA makes up 50% of the weight of a neuron's membrane. I previously mentioned the 2003 study[19] that indicated that a high DHA diet fed to pregnant bitches and their puppies led to an improvement in trainability. Another study[20] found that aggressive dogs had lower serum DHA levels than non-aggressive dogs, indicating the possible beneficial effect on temperament of DHA supplementation.

Supplementation of omega-3 fatty acids has been shown to improve survival times of dogs with lymphoma.[21] Such supplementation also helps dogs with atopic dermatitis.[22, 23] Omega-threes help dogs with hyperlipidemia.[24, 25] They have been shown to help with cardiomyopathy and chronic valvular disease.[26, 27] Supplementation with omega-three fatty acids also aids the treatment of chronic kidney disease[28, 29] and osteoarthritis in dogs,[30-33] as well as IBD[34] and asthma[35] in cats.

Glucosamine/Chondroitin – Joint supplements such as glucosamine and chondroitin provide nutrients that improve the health of the body's articulations. Many studies[36-39] have been published that show that the supplementation of glucosamine and chondroitin, especially in the form of perna mussel, can decrease pain and improve mobility for dogs with osteoarthritis.

Recent research[40] demonstrated that a supplement containing glucosamine and chondroitin actually prevented the development of osteoarthritis in dogs. In the study, 105 healthy Labrador Retrievers were randomly divided into treatment and control groups. In the control group, 33.3% of the dogs developed radiographic evidence of elbow dysplasia compared to 18.5% in the treated group. Symptoms of dysplasia at 12 months differed between the treated (12.5%) and control (61.5%) animals.

Conclusion

The use of supplements is becoming more and more popular. In fact, more than half of millennials, who make up one-third of all pet owners, will try natural remedies before conventional treatments and they have a broader sense of health than simply "not sick."[41-43] Whether you know it or not, many of your clients give supplements. Supplement sales reached $580 million in 2016, up 3.5% from 2015. Sixty-nine percent of dog owners and sixty-eight percent of cat owners rely on their vet for supplement advice. And still, thirty-one percent of dog owners and twenty-four percent of cat owners purchased pet supplements on line.[44] Where do you think it is best for your clients to get their pets' supplements, from Dr. Google or from you?

Both diseased and healthy animals benefit from certain nutritional supplements. In my opinion, the fact that supplementation with these nutrients can help with so many problems indicates that our current diets are deficient and thus predispose pets to these diseases.

References

1. National Research Council (NRC). *Safety of Dietary Supplements for Horses, Dogs and Cats*. Washington, DC: National Academies Press. 2009.
2. Freeman LM, Abood SK, Fascetti AJ, Fleeman LM, Michel KE, Laflamme DP, Bauer C, Kemp BL, Van Doren JR, Willoughby KN. Disease prevalence among dogs and cats in the United States and Australia and proportions of dogs and cats that receive therapeutic diets or dietary supplements. *J Am Vet Med Assoc*. 2006;229(4):531-4.
3. Bookout, W. Khachatoorian LB. "Regulations and quality control" in: *Veterinary Herbal Medicine*, edited by S.G. Wynn and B.J. Fougere. 99-119. St. Louis, MO:Mosby, Inc. 2007.
4. Dzanis DA. "Nutraceuticals and Dietary Supplements" in Applied Veterinary Clinical Nutrition, edited by A.J. Fascetti and S.J. Delaney. 57-67. West Sussex, UK:John Wiley & Sons, Inc. 2012.
5. Angelino PD, et al. Residual alkaline phosphatase activity in pasteurized milk heated at various temperatures-measurement with the fluorophos and Scharer rapid phosphatase tests. *J Food Prot.* 1999;62(1):81-85.
6. Severi S, et al. Effects of home-based food preparation practices on micronutrient content of foods. *Eur J Cancer Prev.* 1998;7(4):331-335.
7. Yadav SK and Sehgal S. Effect of home processing on ascorbic acid and beta-carotene content of spinach (Spinacia oleracia) and amaranth (Amaranthus tricolor) leaves. *Plant Foods Hum Nutr.* 1995;47(2):125-131.
8. Dawson D, Waters HM. Malnutrition: folate and cobalamin deficiency. *Br J Biomed Sci.* 1994;51(3):221-130.
9. Schroeder HA. Losses of vitamins and trace minerals resulting from processing and preservation of foods. *Am J Clin Nut.* 1971;24(5):562-573.
10. Garrison and Somer, The Nutrition Desk Reference, Keats Publishing, 1995;66-145.
11. Ghebremeskel K, Crawford MA. Nutrition and health in relation to food production and processing. *Nutritional Health.* 1994;9(4):237-253.
12. Smith CA. Changes and Challenges in Feline Nutrition, *J Am Vet Med Assoc.* 1993;203(10):1395-1400.
13. Hill R, Common Myths and Mistakes in Veterinary Nutrition, presented at the North American Veterinary Conference, Jan. 2010.
14. Lila, MA. From beans to berries and beyond: teamwork between plant chemicals for protection of optimal human health. *Ann N Y Acad Sci.* 2007;1114:372-80.
15. Jacobs DR Jr, Tapsell LC. Food, not nutrients, is the fundamental unit in nutrition. *Nutr Rev.* 2007;65(10):439-50.
16. Chung JY, Sung EJ, Cho CG, Seo KW, Lee JS, Bhang DH, Lee HW, Hwang CY, Lee WK, Youn HY, Kim CJ. Effect of recombinant lactobacillus expressing canine GM-CSF on immune function in dogs. *J Microbiol Biotechnol*. 2009;19(11):1401-7.
17. Marsella, R., Santoro, D. and Ahrens, K. Early exposure to probiotics in a canine model of atopic dermatitis has long-term clinical and immunological effects. *Vet Immunol Immunopathol.* 2012;2:185–189.

18. Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, Bienenstock J, Cryan JF. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proc Natl Acad Sci U S A*. 2011;108(38):16050-5.
19. Kelley, R. L., et al. "Effect of dietary fish oil on puppy trainability." *Proc International Society for the Study of Fatty Acids and Lipids* (2004): 1-5.
20. Re S, Zanoletti M, Emanuele E. Aggressive dogs are characterized by low omega-3 polyunsaturated fatty acid status. *Vet Res Commun.* 2008;32:225–230.
21. Ogilvie GK, Fettman MJ, Mallinckrodt CH, et al. Effect of fish oil, arginine, and doxorubicin chemotherapy on remission and survival time for dogs with lymphoma: A double-blind, randomized placebo-controlled study. *Cancer.* 2000;88:1916–1928.
22. Mueller RS, Fettman MJ, Richardson K, et al. Plasma and skin concentrations of polyunsaturated fatty acids before and after supplementation with n-3 fatty acids in dogs with atopic dermatitis. *Am J Vet Res.* 2005;66:868–873.
23. Mueller RS, Fieseler KV, Fettman MJ, et al. Effect of omega-3 fatty acids on canine atopic dermatitis. *J Small Anim Pract.* 2004;45:293–297.
24. Bauer JE. Evaluation and dietary considerations in idiopathic hyperlipidemia in dogs. *J Am Vet Med Assoc.* 1995;206:1684–1688.
25. Xenoulis PG, Steiner JM. Lipid metabolism and hyperlipidemia in dogs. *Vet J.* 2010;183:12–21.
26. Smith CE, Freeman LM, Rush JE, et al. Omega-3 fatty acids in Boxer dogs with arrhythmogenic right ventricular cardiomyopathy. *J Vet Intern Med.* 2007;21:265–273.
27. Freeman LM, Rush JE, Markwell PJ. Effects of dietary modification in dogs with early chronic valvular disease. *J Vet Intern Med.* 2006;20:1116–1126.
28. Brown SA, Brown CA, Crowell WA, et al. Beneficial effects of chronic administration of dietary omega-3 polyunsaturated fatty acids in dogs with renal insufficiency. *J Lab Clin Med.* 1998;131:447–455.
29. Brown SA, Brown CA, Crowell WA, et al. Effects of dietary polyunsaturated fatty acid supplementation in early renal insufficiency in dogs. *J Lab Clin Med.* 2000;135:275–286.
30. Fritsch D, Allen TA, Dodd CE, et al. Dose-titration effects of fish oil in osteoarthritic dogs. *J Vet Intern Med.* 2010;24:1020–1026.
31. Fritsch DA, Allen TA, Dodd CE, et al. A multicenter study of the effect of dietary supplementation with fish oil omega-3 fatty acids on carprofen dosage in dogs with osteoarthritis. *J Am Vet Med Assoc.* 2010;236:535–539.
32. Roush JK, Cross AR, Renberg WC, et al. Evaluation of the effects of dietary supplementation with fish oil omega-3 fatty acids on weight bearing in dogs with osteoarthritis. *J Am Vet Med Assoc.* 2010;236:67–73.
33. Roush JK, Dodd CE, Fritsch DA, et al. Multicenter veterinary practice assessment of the effects of omega-3 fatty acids on osteoarthritis in dogs. *J Am Vet Med Assoc.* 2010;236:59–66.
34. Trepanier L. Idiopathic inflammatory bowel disease in cats. Rational treatment selection. *J Feline Med Surg.* 2009;11:32–38.
35. Leemans J, Cambier C, Chandler T, et al. Prophylactic effects of omega-3 polyunsaturated fatty acids and luteolin on airway hyperresponsiveness and inflammation in cats with experimentally-induced asthma. *Vet J.* 2010;184:111–114.

36. Bui LM , Bierer TL. Influence of green lipped mussels (Perna canaliculus) in alleviating signs of arthritis in dogs. *Vet Ther.* 2003;4(4):397-407.
37. Rialland P, et al. Effect of a diet enriched with green-lipped mussel on pain behavior and functioning in dogs with clinical osteoarthritis. *Can J Vet Res.* 2013;77(1): 66-74.
38. Hielm-Bjorkman A, Tulamo R, Salonen H, Raekallio M. Evaluating Complementary Therapies for Canine Osteoarthritis Part I: Green-lipped Mussel (Perna canaliculus). *Evid Based Complement Alternat Med*. 2009;9:365–373.
39. Pollard B, Guilford WG, Ankenbauer-Perkins KL, Hedderley D. Clinical efficacy and tolerance of an extract of green-lipped mussel (*Perna canaliculus*) in dogs presumptively diagnosed with degenerative joint disease. *New Zeal Vet J.* 2006;54(3):114-118.
40. Martí-Angulo S, García-López N, Díaz-Ramos A. Efficacy of an oral hyaluronate and collagen supplement as a preventive treatment of elbow dysplasia. *J Vet Sci.* 2014;15(4):569-574.
41. Arulrajah N. Why – and How – You Should Engage with Millennials. *Veterinarian's Money Digest* 2017;1(4):22-23.
42. Miller, N. 1 in 3 U.S. pet owners millennials: what it means for the pet food market. Packaged Facts website www.packagedfacts.com/Content/Blog/ 2017/02/07/1-in-3-US-Pet-Owners-Millennials-What-it-Means-for-the-Pet-Food-Market. Published February 7, 2017. Accessed January 5, 2018.
43. Goldman Sachs. Millennials coming of age. Goldman Sachs website. http://www.goldmansachs.com/our-thinking/pages/millennials/Accessed April 18, 2018.
44. Packaged Facts. Pet Supplements Market in the U.S., 6th Edition. Apr 13, 2017. https://www.packagedfacts.com/pet-supplements-edition-10747551/