

The Role of Nutraceuticals in Dogs with CDS: Supporting the Nutritional Needs
of Senior Dogs

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Abstract

Canine cognitive dysfunction refers to a neurodegenerative disease in aging dogs, characterized by a gradual decline in cognitive function. Clinically, CDS may cause behavioral changes such as disorientation in the home, altered interactions with owners and people, changes in house training, sleep-wake cycles and reduced recognition of family members. (Manteca, 2011) Improvements in nutrition, medical care and protection from accidental death have resulted in greater longevity, with many companion dogs living well into the elderly stages of life. The prevalence of CDS and its dietary and pharmacological treatment has been widely reviewed as interest in CDS as a welfare issue for elderly pets has grown. (Manteca, 2011). Recent research has provided studies that evaluate the effects of a diet rich with antioxidants on cognitive decline in senior dogs. Some studies of the canine model effectively suggest that oxidative damage impairs cognitive function and that antioxidant treatment can result in significant improvements, supporting the need for further human studies. This paper will examine the role nutraceuticals play in supporting the nutritional needs of aging dogs.

Introduction and Overview

It is known that with increasing age, dogs develop a form of neurodegenerative disease having many similarities to age related cognitive impairment and Alzheimer's disease in humans. (Landsberg, 2005; Neilson, Hart, Cliff and Ruehl, 2001) For dogs as young as seven years of age, a decline in learning and memory has been demonstrated through a variety of neuropsychological tests. Apart from the clinical signs previously mentioned, CDS may cause other symptoms such as anxiety, one of the main underlying factors contributing to behavioral problems in dogs. The impact this has had on the human animal bond is significant. Many of the behavioral changes and medical conditions associated with aging may impair the welfare of the animal. As such, it is vitally important that owners understand and are responsive and sensitive to their pet's subtle

The Role of Nutraceuticals in Dogs with CDS: Supporting the Nutritional Needs of Senior Dogs

changes in behavior as indicators of pain, welfare and quality of life. Interactions that support the human animal bond are critical to supporting the emotional needs of their aging pets. (Landsberg, DePorter, & Araujo, 2011)

Neuropsychological tests that have been developed and validated for the assessment of cognitive decline in senior dogs make it possible to accurately determine whether a particular therapeutic agent is effective at improving learning and memory. (Landsberg, 2005) Laboratory testing also provides an objective measure for controlled studies that can predict the effect of therapeutic intervention in the treatment of cognitive dysfunction in pet dogs, and many therapeutic agents have now been evaluated and approved for use in pets with cognitive dysfunction. Early intervention with a number of drugs, natural products and supplement formulations that have been tested and developed for use in dogs with cognitive dysfunction will support and preserve the human animal bond and the family's relationship with their beloved pet.

Problem Statement and Research Question

Assessing and maintaining cognitive and behavioral well being in senior pet dogs requires special consideration since changes in anxiety levels and cognitive function may be complicated by other medical conditions, medication, sensory perception and previous learning. (Landsberg et al, 2011) Behavioral signs are often the first and sometimes only sign or indication of pain, illness and cognitive decline. Therefore, family members need assistance in recognizing the significance of these changes and the importance of notifying their veterinarian as soon as possible. Early detection of behavioral changes associated with disease may create opportunities for diagnosis, treatment and providing nutritional support, potentially preventing further cognitive decline, increasing longevity, and addressing welfare issues sooner. Animal welfare is defined as being impaired when any of the Five Freedoms are compromised. Many of the behavior changes and medical conditions associated with aging may impair the welfare of the animal as defined by the five freedoms. (Manteca, 2011); as many of these diseases result in pain or interfere with expression of normal behavior. In particular, the main effect of CDS on welfare is that is

The Role of Nutraceuticals in Dogs with CDS: Supporting the Nutritional Needs of Senior Dogs

causes an increase in anxiety and stress. To the extent that this can be prevented or detected early through owner education and the implementation of preventative treatment options that includes nutritional support, the welfare of the geriatric patient may be greatly improved and the human animal bond maintained.

Owners of dogs exhibiting signs of cognitive impairment may find it increasingly difficult to cope with the changes in their pet's behavior, therefore, owner expectations of their elderly pets may not be in alignment with the reality of their pet's experience. This paper will explore the question "How do nutraceuticals and dietary supplements support the nutritional needs of elderly pets, and what role does their use play in prevention and treatment of CDS?" Literature on studies regarding the use of dietary supplements and their effects on free radical damage, improvement of cognitive related function and task completion, and possible effects on behavioral changes will be presented with a discussion of the results. Age related behavioral changes have contributed to the high surrender rate of elderly pets to shelters nationwide. The use of nutritional supplements and nutraceuticals have been found to have efficacy with respect to delaying the effects of cognitive decline and thus, the anxiety that causes development of behavior problems in elderly pets.

Working Hypothesis

The maintenance requirements for senior pet dogs are presumed to be the same as for adult pets by most companion animal owners and caregivers. To the extent that pet dog owners can be educated as to the role and efficacy of nutritional support and environmental needs of their elderly pets, a better understanding of the issues surrounding their senior pet's welfare can be realized. Educating senior pet dog owners will help them understand and recognize behavioral changes associated with cognitive decline, environmental needs of their aging pet dog, and the diet and nutritional requirements of the senior pet dog. These factors, when combined, will improve the welfare of the senior pet dog and reduce the breakdown of the human animal bond so often experienced by owners and their pets, thereby reducing surrenders of elderly pets.

Behavioral Implications: Efficacy Studies for Nutritional Management of CDS

According to Manteca, (2011) diagnosis of cognitive decline can be clinical or based on laboratory tests. Interest in CDS in aging dogs has grown as it has many similarities to Alzheimer's Disease. From a clinical standpoint, behavioral changes include disorientation, altered interactions with family members or other animals, alterations in sleep-wake cycles, changes in activity levels and house soiling, and excessive barking, whining and howling. In his article, Manteca (2011) reviews dietary and pharmacological treatment of CDS. Other studies have reviewed the use of dietary supplements such as Omega 3 and 6 fatty acids, chondroitin complex and glucosamine, Vitamins E and C and their efficacy as a strategy to improve antioxidant defense and reduce the toxic effects of free radicals.

Efficacy of nutraceuticals in the treatment of cognitive decline.

Studies suggest that the use of nutraceuticals as a dietary supplement may prevent cognitive decline in aging pet dogs. (Landsberg, 2005) Nutraceuticals are defined as "any substance that may be considered a food or part of a food and provides medical or health benefits, including the prevention and treatment of disease". (Marwick & Hendricks, 2007) According to Landsberg (2005) the efficacy of a new canine therapeutic diet was assessed over a two- year period using neurological testing procedures. Clinical trials were also performed, wherein the diet was supplemented with a broad spectrum of antioxidants and mitochondrial cofactors that might improve antioxidant defenses, decrease production, improve clearance and thus reduce the damaging effects of free radicals. In aged rodents, antioxidants may improve performance and delay the onset of age related impairment and cognitive decline in humans. (Cotman et al., 2002) It is noted in Cotman et al., (2002) that since the brain has a high rate of oxidative metabolism, high lipid content, and limited ability for regeneration, that it is particularly vulnerable to the effects of free radicals and oxidative damage. In fact, widespread oxidative damage, extensive production of free radicals and low levels of Vitamin E have all been identified in the brains of dogs with dementia. (Head et al., 2002) Oxidation causes damage to lipids, proteins and DNA/RNA. Oxidative stress also induces the

The Role of Nutraceuticals in Dogs with CDS: Supporting the Nutritional Needs of Senior Dogs

expression of APP and may contribute to the misprocessing of APP, resulting in the formulation of amyloid fragments. This in turn results in the loss of compensatory ability. All these factors lead to more amyloid deposits, possible synapse loss and DNA damage. As the pathways ultimately converge, the resulting effect is neuron dysfunction and neuron death. (See Figure 3). (Cotman et al., 2002)

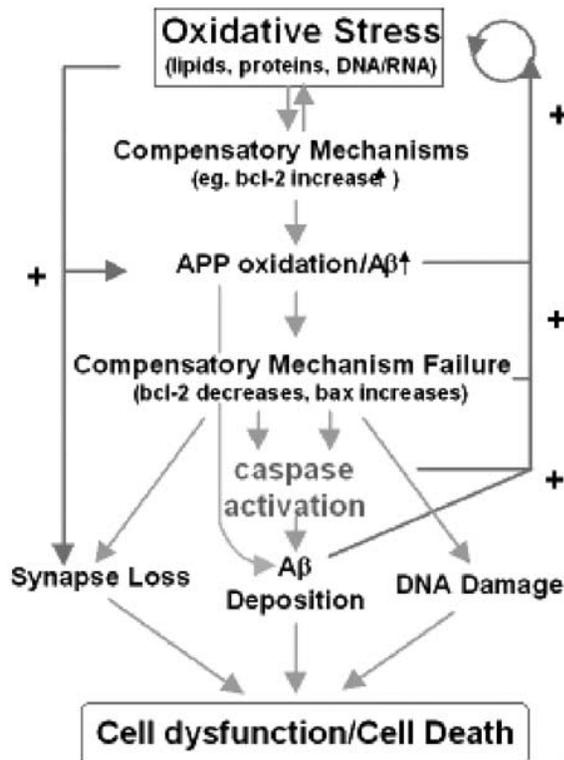


Figure 3. (Cotman et al., 2002)

In studies of the human brain, complications arise due to the presence of neurofibrillary tangles when establishing a link between oxidative damage, amyloid deposition and cognitive function. The aged canine brain, in comparison, develops extensive amyloid deposition due to the absence of tangles. Accordingly, a series of studies were initiated to test the hypothesis that a diet rich in antioxidants can result in improvements in learning and memory in aging canines, as well as reducing the accumulation of pathology in the aged brain. The study was conducted as a random placebo controlled clinical trial. Each dog was tested one year before the start of the trial, wherein old and young dogs were given a series of baseline cognitive tests, which were used to assign animals to

The Role of Nutraceuticals in Dogs with CDS: Supporting the Nutritional Needs of Senior Dogs

cognitively equivalent groups. One of the aged groups and one of the young groups was changed to a food that was identical to the control food, but with the addition of a broad spectrum of antioxidants and mitochondrial enzymatic co-factors while the other groups were maintained on the control food. The animals were maintained on the diet for six months prior to the cognitive assessment. The food was supplemented with a mixture of fruits and vegetables, Vitamins E and C, alpha lipoic acid and L-carnitine (mitochondrial cofactors). The selection process for these agents was based on their mechanism of action and data on measures of serum and urinary oxidative damage in dogs.

Task performance in the oddity discrimination task presented to young and older dogs showed significant statistical differences. As the task became more difficult the older group had an increase in errors identifying the odd item out of three, where two were identical. In each trial, the odd item became more like the other two. Dogs were rewarded when identifying the odd (correct) item. The effects of dietary manipulation showed significant improvement in older dogs on the fortified diet in oddity discrimination, which provided a sensitive measure of age-dependent cognitive deterioration in dogs. The results demonstrate that the age dependent effect may at least be partially reduced by maintenance on a food fortified with a complex mix of antioxidants and mitochondrial enzymatic cofactors. (Cotman, et al., 2002)

In conclusion, it is hypothesized that in the aged canine population, cognitive decline occurs along a continuum, reflecting a similar decline as with humans. In the veterinary literature, the latter phase of cognitive decline is generally classified as CDS defined as memory impairments and losses in activities of daily living such as social interactions, grooming, disruption of sleep–wake cycles. The results of the study suggest that a diet enriched with a combination of antioxidants with mitochondrial enzymatic cofactors may work together synergistically leading to an improvement in learning and memory associated with the progressive decline along the cognitive continuum.

According to Landsberg, (2005), additions to the new prescription diets for prevention of CDS include increased levels of omega-3 fatty acids to promote cell membrane health as well as a possible anti-inflammatory effect (Youdim, 2000; Lands et al., 1990). Vitamins E and C help to neutralize free radicals and prevent damage to cells and cell membranes (Fryer, 1998; Mayes, 2000; Packer, 1994; Kamal-Eldin and

The Role of Nutraceuticals in Dogs with CDS: Supporting the Nutritional Needs of Senior Dogs

Applqvist, 1996; Joseph et al., 1998). Landsberg (2005) notes that the supplemented diets were shown to improve performance on a number of cognitive tasks. When compared with non- supplemented diets, improved performance on a landmark discrimination test was seen as early as 2-8 weeks after the start of therapy, continuing through six months on an oddity discrimination- learning task. In addition, in a 60 day double blind clinical trial of 142 dogs, there was a significantly greater improvement in cognitive signs in the group on the fortified diet (Prescription dietR Canine b/dR) than in the control group. (Dodd et al., 2003)

Efficacy of Nutraceuticals with CDS Related Behavior Change

According to Landsberg, (2005) clinical cases of CDS are seldom identified in pet dogs until the age of 11 years, mainly due to the behavioral changes noticed by aging pet dog owners. These include a sudden change in interactions with family members (including aggression that seems out of context), a decrease in activity levels, excessive vocalization and a change in house soiling behavior and sleep wake cycles, such as roaming around late at night and being unable to settle. Tests of learning and memory are unlikely to have revealed memory deficits or other signs of cognitive impairment in most senior pet dogs, whereas, dogs used for bomb detection and agility trained performance dogs might be noticed to have a decline in cognitive function at an earlier age. CDS in senior dogs has been characterized as a decline in cognitive function affecting learning, memory, perception, and awareness, thus the acronym DISHA has been applied to describe the clinical behavioral symptoms: disorientation, altered interactions with people or other animals, sleep wake cycle alterations, house soiling and altered activity levels. Loss of awareness and memory of people and places can result in an increase in anxiety levels, wherein senior dogs develop separation anxiety, fear and phobias not previously observed. Psychopharmacological treatment has become an avenue of treatment for behavioral disorders. However, many dog owners are concerned about undesirable side effects, substance abuse, and withdrawal reactions.

Tryptophan-induced serotonergic activity in the brain has been implicated in the regulation of many behavioral processes such as mood, aggression, and susceptibility to

The Role of Nutraceuticals in Dogs with CDS: Supporting the Nutritional Needs of Senior Dogs

stress (Leathwood, 1987; van Hierden et al., 2004 ; Koopmans et al., 2005; In Kato, 2012.). In a study by Kato, Miyaji, Ohtani and Ohta (2012) the effects of a diet (CALM CANINE) supplemented with alpha-casozepine and *L*-tryptophan on the stress response of anxious dogs were evaluated, with a focus on anxiety-related behavioral parameters and physiological parameters. In the study, forty -four dogs were fed a control diet followed by a study diet; each for an eight week period. There was a transitional period of one week between diets. After seven weeks on a particular diet, owners were asked to report on their dog's behavior by completing a behavioral questionnaire. The Canine Behavioral Assessment and Research Questionnaire was used, with the results showing effects of the study diet to be significant for 4 anxiety related behavioral parameters. After 7 weeks on each diet, the urine cortisol-to-creatinine ratio (UCCR) was measured to assess the stress response to a visit to a veterinary practice for toenail clipping. This measurement was taken to complement the behavioral data with regard to how susceptible the dogs were to stress. There was a positive correlation found between home measured, baseline UCCR rates and post-stressor UCCR. The stressor induced increase was significantly lower in dogs fed the study diet when compared with the control diet. It was noted that the supplementation of casozepine or the proportion of protein in a given diet could be a determining factor. (Kato et al., 2012) During the study period, no adverse effect was observed in any of the dogs. The study found that the supplemented study diet seemed to improve the individual's ability to cope with stress and therefore may reduce anxiety related behavior in anxious dogs. Further studies are needed to investigate whether the observed effects were due to the effects of tryptophan alone, casozepine alone, or combined effect of the both. It is noted that in addition to owner preference for dietary applications to support behavioral changes and the nutritional needs of their aging pets, treatment through diet can be more easily achieved as a regular daily event that is easier to administer than medications. (Kato et al., 2012)

In a study on dogs by Milgram, Head and Zicker et al. (2004), a senior diet (Canine b/d, Hills Pet Nutrition) has been shown to improve the signs and slow the progress of cognitive decline. The diet is supplemented with a combination of fatty acids, antioxidants (vitamins C and E, **b**-carotene, selenium, flavonoids, and carotenoids), as well as DL-**a**-lipoic diet and L-carnitine, which are intended to enhance mitochondrial

The Role of Nutraceuticals in Dogs with CDS: Supporting the Nutritional Needs of Senior Dogs

function. In the study, the effectiveness of two interventions were tested on aging beagles, along with a group of younger dogs and controls. The two interventions were a diet fortified with antioxidants as previous outlined, and a program of behavioral enrichment. This was a longitudinal study with baseline cognitive protocol testing showing equivalent results within all four select groups. Results demonstrated that behavioral enrichment or dietary fortification with antioxidants over a long-duration can slow age-dependent cognitive decline, and that the two treatments together are more effective than either alone in older dogs. (Milgram et al., 2005)

Categories of clinical behavioral symptoms previously described (DISHA) do not necessarily make up all clinical signs which might be associated with cognitive decline in dogs, since other signs have been reported including an increase in anxiety, a decrease in self hygiene and grooming, altered appetite, decreased responsiveness to stimuli and decreases in learning and memory. (Landsberg & Ruehl, 1997; Landsberg et al., 2003) The distribution of behavior problems in older pet dogs may be represented by a case-load of referrals to veterinary behaviorists, which may give some idea as to the most common behaviors of concern to pet owners. In a study of dogs aged 9 years or older, these included separation anxiety (29%), aggression toward people (27%), house soiling (23%), excessive vocalization (21%), phobias (19%), waking at night (8%), compulsive or repetitive behaviors (5%), and intraspecies aggression (5%). (Landsberg & Araujo, 2005)

Complementary Nutraceutical and Supplement Therapies for Treatment of CDS

Additional complementary therapies have been recommended in treatment of CDS in aging dogs that include the use of nutraceuticals, herbal extracts and vitamins, and have been advocated for use in pets to help calm, reduce anxiety and induce sleep. These include melatonin, valerian root, Bach's flower remedies, and DAPR (Veterinary Products Laboratories, Phoenix, AZ), which is a synthetic pheromone modeled upon pheromones secreted from the sebaceous glands of the inter-mammary chains of the lactating bitch. (Landsberg, 2005) These complementary products contain a mix of vitamins and nutraceuticals in addition to herbal ingredients; including phospholipids,

The Role of Nutraceuticals in Dogs with CDS: Supporting the Nutritional Needs of Senior Dogs

fatty acids, antioxidants and mitochondrial co-factors that might, in theory, be complimentary or synergistic in their actions. Many of these are known to be useful for their antioxidant properties and for their anti-inflammatory properties in the treatment of cognitive decline. For example, Phosphatidylserine is a phospholipid that constitutes a major building block of the cell membrane. It has been reported to improve scores for activity, social interactions, memory and learning in humans with cognitive decline. (Crook et al., 1991, 1992) B Vitamins (Niacin, Thiamine, B6, B12, and riboflavin) also have neuro-protective effects and antioxidant properties, as well as the ability to normalize neurotransmitter levels. (Landsberg, 2005) Ginkgo biloba may improve memory loss, fatigue, anxiety, and depression in the elderly, possibly because of MAO inhibition, free radical scavenging, or enhancement of blood flow. There is some evidence that Ginkgo biloba may improve memory loss, fatigue, anxiety, and depression in the elderly as well as delay the progression of Alzheimer's in humans. It is noted that some of these therapies have not been tested in a clinical or laboratory setting, however, they provide an alternative, and relatively safe, treatment in senior pet dogs that is refractory to standard therapies (Landsberg, 2005)

Chondroitin sulphate and glucosamine use in the treatment of degenerative joint disease

Since many aging dogs suffer from osteoarthritis, discussion of the supplemental use of chondroitin sulphate and glucosamine in the treatment of degenerative joint disease in aging dogs with CDS has some significance. Pain associated with joint degeneration may exacerbate the condition and behavior of the senior pet dog in a case of cognitive decline, and therefore this supplement can be beneficial in relieving joint pain associated with osteoarthritis. Chondroitin sulfate, the primary glycosaminoglycan in cartilage, is frequently combined with glucosamine in commercial preparations. Chondroitin sulfate reduces the osteoarthritic breakdown of cartilage by competitively inhibiting metalloproteases and by decreasing complement activation and histamine-related inflammation (2, Runyon CL personal communication 2002; in Harasen, 2005). There is considerable evidence on the use of glucosamine and chondroitin sulphate as chondroprotective agents (Lippiello et al., 1999) in experimentally-induced degenerative

The Role of Nutraceuticals in Dogs with CDS: Supporting the Nutritional Needs of Senior Dogs

joint diseases in dogs (Canapp et al., 1999). There are also many testimonial surveys that have investigated the use of chondroitin sulphate and glucosamine in the treatment of degenerative joint disease that have been conducted (Anderson et al., 1999; in Markwick & Hendricks, 2007)) Benefits include a reduction in symptoms such as tenderness around the affected joint, pain on walking, pain on standing, joint swelling and spontaneous pain.

Discussion

Efficacy for the use of nutraceuticals in the nutritional support of senior pet dogs with indications of CDS has been demonstrated through clinical and laboratory settings, although some alternative therapies require additional investigation. (Kato et al., 2012) Advances in nutrition for the pet food industry have made it easier for the pet dog owner to research and provide healthful nutritional alternatives to standard commercial foods, with the additional benefit of adding supplements and nutraceuticals to support the nutritional needs of aging and senior pet dogs. Many products on the market today provide for supplements that have shown efficacy in improving performance of senior dogs, and maintaining those changes over time. (Landsberg et al. 2011) The results achieved thus far demonstrate that the use of dietary supplements is a strategy in treating cognitive decline that is not only preferred by owners to treatment with psychopharmaceuticals, but that will, in fact, reverse the effects of cognitive decline in clinical settings and reduce anxiety levels that result form loss of awareness and recognition of familiar people and places. Importantly, nutritional support with nutraceuticals has shown better efficacy when combined with behavioral enrichment programs. (Milgram et al., 2005) Landsberg et al. (2011) notes that the assessment and consideration of senior dogs' quality of life warrants careful consideration, in that changes in anxiety and cognitive function may be compounded by other medical conditions, sensory perception, concurrent medications, previous learning and pain. While the behavioral signs of cognitive decline such as are easier to observe, the caregiver must also take into consideration the effects of medical problems that contribute to the dog's welfare and quality of life. Landsberg notes that diagnoses of age related behavioral problems are under diagnosed and affect a large population of senior

The Role of Nutraceuticals in Dogs with CDS: Supporting the Nutritional Needs of Senior Dogs

dogs. (Landsberg et al., 2011) Kato (2012) adds that veterinarians may consider dietary strategies as a solution for the management of anxiety-related problem behavior in dogs.

It would behoove the professional behaviorist to incorporate a CDS information guide and summary that includes nutritional and environmental needs for aging pet dogs to their owners. Behaviorists faced with confirming age related behavioral diagnoses should work with their client's veterinarian in conjunction with the process of a professional consultation for behavioral issues in order to rule out medical causes for the reported behavior problems. Part of this process should include nutritional education to effectively support the needs of the aging pet dog.

The Role of Nutraceuticals in Dogs with CDS: Supporting the Nutritional Needs of Senior Dogs

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The Role of Nutraceuticals in Dogs with CDS: Supporting the Nutritional Needs of Senior Dogs

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The Role of Nutraceuticals in Dogs with CDS: Supporting the Nutritional Needs of Senior Dogs