Scientific Review

Integrative Treatment of Canine Cognitive Dysfunction

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Abbreviations

Aβ	Amyloid-β
AD	Alzheimer's disease
CBD	Cannabidiol
CCD	Canine cognitive dysfunction
DISHAA	Disorientation; social Interactions; Sleep-wake cycles; House soiling, learning, and memory; Activity; and Anxiety
GBA	Gut-brain axis
MCT	Medium-chain triglyceride
SAMe	S-adenosyl-L-methionine
SCFA	Short-chain fatty acid
TCVM	Traditional Chinese Veterinary Medicine

Abstract

Canine cognitive dysfunction (CCD) has been called the canine analogue of human Alzheimer's disease (AD). It is more common than previously believed and affects 14% to 35% of the pet dog population, with a prevalence of 14% to 68% in dogs older than 8 years of age. The hallmark of this disease is slowly progressive deterioration of cognitive abilities and behavioral changes. Confusion, anxiety, interruption of the sleep-wake cycle, and decreased interaction with the owner are common manifestations of this syndrome in dogs. The pathophysiology involves cerebral inflammation and vascular disease, deposition of amyloid plaques, oxidative brain injury, and mitochondrial dysfunction. There is no cure for CCD, but there are many proven therapeutic interventions available to the integrative practitioner, which have the best outcome when instituted early in the course of the disease. Dietary therapy, nutraceuticals, physical therapy, cognitive enrichment, acupuncture, and herbal therapy are all used to slow the progression of this neurodegenerative disease.

Introduction

Canine cognitive dysfunction (CCD) is a common medical condition that occurs in dogs older than 8 years of age (1-3). It is akin to canine dementia and is considered the canine analogue of human Alzheimer's disease (AD) (1-3, 8-11). The disorder is characterized by slow deterioration of cognitive abilities associated with altered mentation and dementia. In older dogs, this manifests as behavioral changes, such as disorientation, loss of house-training and other learned behaviors, changes in sleeping patterns, changed or altered interaction with family members and other pets, and alterations in anxiety and activity (1-7, 9). The acronym DISHAA, which stands for **D**isorientation; social **I**nteractions; **S**leep-wake cycles; **H**ouse soiling, learning, and memory; **A**ctivity; and **A**nxiety, has been developed as a tool to help small-animal practitioners and pet owners with early diagnosis of this condition (1, 10). CCD begins much earlier in life than previously suspected, and veterinarians can play a key role in diagnosis and client education regarding early detection. Preventive measures should be considered when the dogs are

middle-aged to ward off clinical signs and the effects of progressive cognitive decline (8). Integrative practitioners are often asked to treat these patients because conventional pharmaceuticals and interventions may not provide complete relief from this syndrome. Within the veterinary community, there are many misconceptions about CCD in regard to general pathophysiology, prevalence, treatment, and relevance of the disease. According to Dewey et al., the top 3 misconceptions about CCD are that normal canine aging causes mild cognitive impairment, CCD is uncommon, and there are no effective treatments (1). The purpose of this paper is to highlight the available literature and summarize the pathophysiology, characteristics, and available treatments for the integrative practitioner.

Prevalence and Pathophysiology of CCD and AD

CCD is an age-related disorder that is similar to AD in humans and occurs in older dogs. It has been estimated that the prevalence of CCD is between 14% and 35% of the companion dog population (1-3, 7). It is unknown whether CCD is increasing in the pet dog population, although with dogs living longer, it is speculated that this is the case. Although Salvin and colleagues estimated the prevalence of CCD to be 14.2% in dogs older than 8 years of age, they also found that only 1.9% of the dogs had a previous CCD diagnosis from a veterinarian (7). It is therefore likely that veterinarians and clients are dismissing the signs of CCD as a function of normal canine aging (1-12). As with people with AD, the prevalence of CCD dramatically increases with age, with a recent study showing 28% of dogs 11 to 12 years of age and 68% of dogs 15 to 16 years of age suffering from CCD (1-10). Bain and coworkers found that 22% of the dogs in their study did not have clinical signs initially but developed them 12 to 18 months later, whereas 48% of the dogs with impairment in 1 category displayed impairment in 2 or more categories during the same time period (13). The pathophysiology of both CCD and AD involves brain vascular disease and the accumulation and aggregation of amyloid-β (Aβ) peptide. Aβ, a neurotoxic protein, accumulates as plaques in the forebrains of dogs with CCD and people with AD, where it causes neurodegeneration (1, 2, 8, 10, 11). However, dogs usually do not show the severe cognitive impairment seen in humans with AD (9). According to Dr. Elizabeth Head from the Center on Aging at the University of Kentucky, the severity of CCD is determined by the extent of Aβ deposition in the brain (12). The deposition of Aβ is a hallmark for both AD and CCD, making the canine the best naturally occurring animal model for studying human AD (1, 2, 9, 12, 14-16).

The pathophysiology of CCD and AD is complex and multifactorial. Pathologic similarities exist between the brains of people with AD and dogs with CCD (1, 2, 9, 15). Ventricular dilatation, meningeal thickening, gliosis, and cerebral vascular changes occur in both species (1, 11, 14). Decreased cerebral blood flow is an important facet of the pathogenesis of CCD (1, 2). Many of these changes have to do with cerebral vascular disease related to Aβ accumulation around blood vessels and in neurons. Several studies have shown that these proteins interfere with synaptic function because they are highly toxic (2, 11, 12, 14-16). In addition to these toxic Aβ proteins, some histological studies have shown an intraneuronal accumulation of hyperphosphorylated microtubular-associated proteins called *tau proteins* (17). These proteins are a precursor to neurofibrillary tangles, which are found in the brains of AD patients but not in CCD patients (1, 2, 11). It is postulated that canines do not live long enough to develop mature neurofibrillary tangles, but nevertheless, the development of tau protein indicates mitochondrial dysfunction (2, 9-12).

There are many forms of CCD, and often they involve depletion of neurotransmitters or disruption of neuronal pathways. All cases of neurodegeneration and cognitive decline involve oxidative stress and mitochondrial dysfunction.

Mitochondrial dysfunction is central to the development and progression of AD and CCD (18-20). Mitochondria are responsible for producing adenosine triphosphate (ATP), the energy for all cellular functions. The mitochondria undergo functional and morphological changes (including gene expression), some of which is attributed to Aβ deposition. A mitochondrial-mediated impairment of autophagy potentiates Aβ deposition (1, 17). When the cell is unable to catabolize proteins due to defective mitochondria, proteins are deposited as plaques, and there is an intraneuronal accumulation of tau proteins. Tau proteins belong to a family of microtubular proteins located within the neurons (17, 18). During neurodegenerative diseases, tau proteins undergo hyperphosphorylation and accumulate within the neurons, interfering with neurotransmission. Normally, the mitochondria have the ability to decrease the toxic effect of Aβ on cellular function; however, this function diminishes as the mitochondria decline (1). The declining mitochondria have a decreased ability to generate cellular energy in the brain, and the neurons affected by AD and CDD have an impaired ability to uptake and use glucose (1, 17-19).

An imbalance of neurotransmitters in the brain has been documented in both AD and CCD. This imbalance may consist of damage and depletion of dopamine and altered cholinergic transmission, a disruption of the serotonergic pathway,

noradrenergic transmitter disruption, and glutamate-mediated excitotoxic neuronal damage (1, 2, 9, 11, 16, 17). Excessive stimulation of the glutamate receptors—that is, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and *N*-methyl-D-aspartate (NMDA) receptors—contributes to neuronal excitotoxicity and death. Additionally, impairment of the function of inhibitory interneurons adds to the impaired neuronal network of AD and CCD patients (1, 2). Of all of these changes, cholinergic dysfunction has the highest and most consistent relationship to the development of CCD and AD. According to Dewey and colleagues, other abnormalities that are found consistently in the brains of AD and CCD patients include elevation of acetylcholinesterase, resulting in cholinergic decline; increase in monoamine oxidase (MOA) B, which catalyzes the breakdown of dopamine and allows free radicals to form; and elevated CSF levels of lactate, pyruvate, and potassium (1).

Astrocytes and microglia are the main immune cells in the CNS. Both of these cells function to reduce the production of Aβ and remove it before formation of senile plaques can occur. In early AD, large numbers of microglia accumulate to slow down the deposition of Aβ (1, 11, 12, 21). However, this deposition continues, suggesting that the ability of the microglia to clear Aβ declines with age. The failure of the microglia to perform their function appears to be a direct result of the Aβ-induced inflammatory response (21-23). Tumor necrosis factor-α (TNF-α) is a proinflammatory cytokine produced by the microglia that up-regulates Aβ production so the microglia, which were recruited to clean the Aβ protein from the brain, end up promoting the deposition of plaques (21). Astrocytes and microglia are responsible for uncontrolled neuroinflammation that is associated with the progression of both AD and CDD (22).

Involvement of the Gut-Brain Axis in Cognitive Dysfunction

The gut-brain axis (GBA) is an interactive network between the brain and the gut that is composed of neural, immunological, and endocrinological mediators. The GBA is mediated by the enteric nervous system, the CNS, and the intestinal microbiota. The vagal and spinal afferent nerves connect the gastrointestinal (GI) tract to the brain, and efferent sympathetic and parasympathetic fibers run from the brain to the GI tract (24-28). The main modulator of physiological stress is the hypothalamic-pituitary-adrenal (HPA) axis. The HPA also modulates alimentary function (24). Corticotrophin-releasing factor is released by the hypothalamus, affecting intestinal motility, permeability, and inflammation. Bacterial metabolites, such as short-chain fatty acids (SCFAs), GABA, and serotonin precursors, affect the brain via the enteric nervous system. These stimulate the sympathetic nervous system and affect learning and memory (27, 28).

In humans, neurodegenerative disorders such as AD have been linked to dysfunction of the GBA. A number of studies have shown a link between gut microbiome dysbiosis (as a result of antibiotic exposure, dietary change, or illness) and an aggregation of Aβ plaques in the intestinal and CNS cells (25-27). It has been suggested that the bacterial amyloid proteins overlap structurally with human Aβ proteins and induce a molecular mimicry, an immune response to self-antigens (in this case, cerebral Aβ proteins), which ultimately causes a greater inflammatory response in the brain to Aβ proteins due to altered gut microbiome (24). Alternatively, some species of bacteria have been shown to increase levels of SCFAs by digesting dietary fiber in the colon. SCFAs stimulate the release of serotonin from the sympathetic nervous system. Serotonin influences the CNS and has a positive effect on learning and memory (24, 28). When SCFAs are catabolized to ketone bodies, an alternative source of ATP is provided to the brain, which is helpful for patients with glucose dysmetabolism as the result of AD. Perhaps more importantly, studies have shown that low levels of SCFAs negatively affect the immune system and the function of the CNS and peripheral nervous system (24, 27). The gut microbiome of dogs is similar to that of humans, and it has been suggested that nutritional supplements may improve some of the cognitive symptoms in dogs with CCD, although further research is needed (28).

History, Clinical Signs, and Diagnosis

The typical CCD patient is a geriatric dog (older than 8 years of age) with a slowly progressive history of cognitive decline over several months. No association has been found with body size, breed, or sex (1, 2).

Six main clinical features are apparent according to the DISHAA test (1, 10, 17):

1. Disorientation in home and yard
2. Changes in social interactions with human family members
3. Decline in house-training
4. Alterations in sleep-wake cycles
5. Alterations in activity levels
6. Alterations in anxiety levels

A dog must have signs of dysfunction in more than 1 category to be considered for a diagnosis of CCD. Dogs with only 1 category affected may have cognitive decline (10). Like humans with AD, dogs with CCD may show anxiety,

abnormal mentation, compulsive circling, absent or inappropriate response to visual stimuli, and resistance to even minimal restraint (2, 29, 30). Transient vestibular episodes and recent onset of seizure activity are seen in AD, and some veterinary neurologists believe these may also indicate CCD (2, 29, 30) (a). Some of these clinical signs can be seen in dogs with other neurological illnesses, such as brain tumors or geriatric vestibular disease, which can make the diagnosis difficult. Although the DISHAA test was developed to screen for CCD, it is still a diagnosis of exclusion (1, 10, 16, 17). Medical conditions must be ruled out in order to make a definitive diagnosis of CCD. These problems may include, but are not limited to, hyperadrenocorticism, parathyroid disorders, thyroid disorders, diabetes mellitus, chronic kidney disease, cancer, cardiovascular disease, incontinence, liver disease, musculoskeletal disease, dental disease, prostatic disease, sensory loss, intracranial neurological disease, and other painful conditions. MRI diagnosis for CCD is rarely done in dogs due to possible anesthesia complications, cost, and false-negative results (1, 2). Sometimes dogs that have clinical signs of CCD will have a normal MRI, and conversely, dogs whose MRIs show an aging brain may have no signs of CCD. A recent study using MRI showed that dogs with CCD had significantly smaller total hippocampal volumes compared with successfully aging control dogs (31). This knowledge may help in the diagnosis of CCD.

Behavioral problems that look like CCD may include generalized anxiety, separation anxiety, fear-related aggression, pain-related aggression, noise or storm phobias, lack of house-training, attention-seeking behaviors, and compulsive disorders (32). Often, there will be concurrent behavioral and medical illness because medical and cognitive disorders may exacerbate existing, previously undiagnosed behavior problems.

Treatment Overview

There is no known cure for CCD. Therapeutic approaches are multiple and varied and are aimed at improving cognitive function or delaying cognitive decline (1, 2, 17). It is important to remember that certain diseases may increase progression of CCD and AD by accelerating brain aging (33-37). Examples include diabetes, osteoarthritis, hypothyroidism and hyperthyroidism, obesity, Cushing's disease, chronic kidney disease, periodontal disease,

congestive heart failure, pancreatitis, cardiomyopathy, liver disease, seizures, stress, and chronic infection. Major disease is a significant risk factor for cognitive decline and progression of AD, and because many of these diseases are diseases of chronic inflammation, they contribute to brain aging and thus to the progression of CCD (10, 33-37). When treating diseases, it is important to consider the impact any drug or herb will have on the disease progression. For example, dogs with neuropathic pain receiving gabapentin could be switched to amantadine because it has similar effects (dopamine agonist) but also has positive benefits for CCD. Minocycline is also effective for neuropathic pain, and it reduces microglial inflammation (33, 38-40). Zonisamide and potassium bromide do not increase symptoms of CCD (33), but phenobarbital can have detrimental effects in AD patients. A small pilot study in dogs showed that antiepileptic drugs had no effect on CCD scores (41). This is surprising given that antiepileptic drugs, particularly phenobarbital, have been shown to increase AD in humans (42). Until more research is available, is it prudent to avoid antiepileptic drugs when treating epileptic dogs who have concurrent CCD.

When anesthetizing CCD patients, the use of propofol is preferred to gas anesthesia and the use of glycopyrrolate to atropine (43). When possible, all drugs that increase cognitive decline should be removed from the patient and alternatives recommended. A partial list of drug classes to avoid would include barbiturates, benzodiazepines, anticholinergics, chemotherapeutic agents, isoxazoline parasiticides, corticosteroids, and gas anesthesia (33, 43-45). The pros and cons of using benzodiazepines in CCD and AD will be discussed in the next section.

In humans, other conditions can worsen AD, and this is thought to be true of CCD. Lack of exercise, high-carbohydrate diets, excess calorie intake, obesity, and omega-3 and B vitamin deficiencies are thought to play a role in the progression of both AD and CCD (1, 2, 46-48).

Drugs

L-deprenyl, or selegiline, is the only FDA-approved veterinary drug in the United States for the treatment of CCD (17). Selegiline is a selective and irreversible inhibitor of MAO B. It may enhance dopamine and other catecholamines in the cortex and hippocampus and be neuroprotective, possibly by reducing free radical production and/or increasing enzymes that scavenge free radicals, such as superoxide dismutase and catalase (49). Existing studies show improvement in signs of cognitive dysfunction with selegiline, but there is some controversy because most of these studies are based on owner responses to questionnaires rather than standardized comparative cognitive testing (1, 50, 51). Some clinicians feel that the owner responses may not be based on true improvement in cognitive abilities but rather on the fact that selegiline increases brain catecholamines and this can produce nonspecific low-level hyperactivity (1). The recommended dose for selegiline is 0.5 to 1.0 mg/kg PO *q* 24 hours, generally given in the morning, particularly in dogs that have sleep pattern disturbances because it acts as a stimulant and may worsen agitation (49). There is variability in response, with most dogs responding within 2 weeks or slightly longer. In clinical trials, 77% of dogs had a favorable response within 30 days (50). The most improvement was seen in dogs that had disorientation and decreased interaction with family members. Dogs whose clinical signs were loss of house-training or changes in activity or in sleep-wake cycles showed the least improvement (50). Concurrent use with other MAO inhibitors (eg, amitraz, opioids, and tricyclic or other antidepressants) and SSRIs should be avoided because these drugs have the potential to cause serotonin syndrome. Reported adverse effects include restlessness and agitation, vomiting, disorientation, diarrhea, diminished hearing, increased destructive behavior in dogs with separation anxiety, anorexia, anemia, stiffness, and polydipsia. Some dogs may show increased signs of aggression (49). Selegiline is not an effective drug in human AD patients (1, 2).

Other drugs have been used to treat or improve CCD. NSAIDs may improve CCD by reducing brain inflammation (1). Amantadine, an NMDA receptor antagonist, has been shown to have benefits for AD in humans by enhancing the noradrenergic system (10, 52). Amantadine is currently used as an alternative to treating neuropathic pain in dogs, but studies on its efficacy for CCD are lacking. Minocycline reduces microglial inflammation and is neuroprotective in several models of animal neurogenerative diseases (33, 39, 40). It is also effective for neuropathic pain. Studies in CCD are also lacking for this drug. Some serotonergic drugs, such as trazodone or fluoxetine, may be used off label to treat some of the symptoms of CCD (1, 10, 17, 53).

Benzodiazepines—in general, CNS depressants—have been shown to worsen signs of AD and increase cognitive loss because they promote neuroinflammation and can inhibit the signaling of the brain insulin receptor, thus decreasing uptake of glucose by the mitochondria (44, 45). Nevertheless, some clinicians have used them successfully on a short-term basis for agitated dogs (10, 53, 54). They may also be used on a case-by-case basis to improve sleep in patients with altered sleep-wake cycles that do not respond to sleep-inducing nutraceuticals, such as melatonin (54).

Other drugs used by veterinary behaviorists and other clinicians treating CCD include propentophylline, adrafinil, and nicergoline. Propentophylline has been used in Europe for older dogs with depression and lethargy. It increases blood flow to the brain and may have neuroprotective properties (10, 53, 54). Adrafinil enhances the noradrenergic system and may be useful in older dogs in maintenance of a normal sleep-wake cycle and to help improve alertness. However, safety and efficacy studies in the canine are lacking (10, 53, 54). Nicergoline, which acts on dopamine and serotonin receptors, is used to promote cerebral vasodilation and has been used in Europe to treat sleep disorders and diminished vigor in canines. However, it is not marketed in North America, and pharmacologic effects have not been published (54).

Diet and Nutraceuticals

In both human AD and CCD of dogs, diet and dietary supplements have a substantial impact on both the development and progression of cognitive decline (1, 3). High-carbohydrate diets, excessive calorie intake, hyperglycemia, obesity, omega-3 deficiencies, and B vitamin deficiencies will contribute to the progression of AD and CCD (46-48, 55, 56). Nutrients that are often deficient in such individuals include B vitamins (eg, B_{12}), vitamin C, vitamin E, mitochondrial cofactors (eg, L-carnitine, DL-α-lipoic acid), and carotenoids from green leafy vegetables. There are specific dietary recommendations for the prevention and treatment of AD. These include a diet rich in plant-based foods, soy protein, antioxidants, probiotics, omega-3 polyunsaturated fatty acids, whole grains, fruits, vegetables, nuts, foods enriched with medium-chain triglycerides (MCTs), and fish. The risk of cognitive decline in humans increases when red meats, poultry, refined sugar, processed food, and high-fat dairy products are added to the diet (1, 46). In the canine, diets high in processed carbohydrates and saturated fats can promote inflammation and increase the risk of cognitive decline (33). The addition of carotenoids and flavonoids as natural antioxidants from fruits, and particularly vegetables, has been associated with improvements in CCD (1, 2, 10, 17). These antioxidants are much more than just antioxidant in their actions. They can also act as mitochondrial cofactors and increase cellular endogenous antioxidant up-regulation (12, 18, 19). Fresh, balanced, homemade, less processed diets containing lean meats or fish and an abundance of fruits and vegetables are advantageous for dogs with CCD (1).

Commercial diets for treatment and prevention of CCD are available (1, 48, 57). These diets are high in MCTs and have added carnitine, lipoic acid, long-chain omega-3 polyunsaturated fatty acids, vegetable-based carotenoids, vitamin E, and vitamin C (2, 3, 48, 57). Homemade diets that are low in high-glycemic carbohydrates and balanced with antioxidants and MCT oil seem to be effective. MCTs are recommended in dogs with CCD, either as part of a formulated diet or a supplement, for several reasons (1). The AD and CCD brain has an impaired ability to use glucose, the brain's main energy source. MCTs provide an alternative energy source, in the form of ketone bodies, for the brain of cognitively impaired patients. MCTs are converted by the liver to the ketone body β-hydroxybutyrate for improved energy metabolism and mitochondrial function in the aging brain. These ketone bodies are rapidly converted to glucose precursors through interactions of astrocytes and glial cells with the surrounding neurons. Although this has been proven in humans, it may be suspect in dogs because, unlike humans, they do not generate ketones uniformly, and some other mechanism may be at work (1, 26). Dogs will generate some ketone bodies when supplemented with MCT oil but do not become ketotic (58). Nevertheless, supplementation with MCT improves learning and memory in aged dogs (10). It is thought that the MCTs may be involved in mitochondrial biogenesis and provide ketones locally to astrocytes for metabolism while not creating systemic ketosis (1, 2). MCTs also improve brain mitochondrial activity and decrease the level of brain amyloid precursor proteins (48). MCTs are commonly included in ketogenic diets for both people and dogs. In one study, a proprietary mix of MCTs was shown to improve cognitive function in aged Beagle dogs when incorporated into commercial food at 5% of the dry matter (48). Foods rich in MCTs are limited to only coconut and palm kernel oils. However, a nutraceutical MCT oil that is 100% MCT is recommended because coconut and palm kernel oil themselves may not contain therapeutic amounts. Proponents of these oils suggest using them at approximately 5% of the dry matter in the diet, initially as top dressing on a commercial food or by using coconut oil as a fat source in a properly formulated home-prepared diet. This amount of coconut or MCT oil should provide between 10% and 5% of the caloric content of the diet, respectively; however, the additional oil can create imbalances in the diet or diarrhea, particularly if extra treats are being given. Total calories are important to consider when adding MCT oil (1).

Nutraceuticals have been used to treat both CCD and AD. Oral *S*-adenosyl-L-methionine (SAMe) was shown to be effective in improving mood and cognitive dysfunction in AD patients (59). One canine study showed that SAMe improved the signs of age-related dementia in 41% of dogs older than 8 years of age (60). Mitochondrial dysfunction, a known cause of CCD and AD, is often associated with pore opening in the mitochondrial outer membrane, known as the *mitochondrial permeability transition port*. Supplements or drugs that close the pore are highly effective in reducing mitochondrial damage and cell death and can reduce neurodegeneration. Apoaequorin is a supplement derived from jellyfish that acts as a mitochondrial permeability transition pore blocker and has been used to treat both AD and CCD (1, 10, 61).

Other nutraceuticals that have been used to treat both CCD and AD include omega-3 fatty acids, particularly docosahexaenoic acid (DHA), valerian root (*Valeriana officinalis*), resveratrol, melatonin, and gingko (*Ginkgo biloba*) (10, 54, 62). Some of these may have the effect of normalizing the sleep-wake cycle and decreasing anxiety. Several supplemental products that contain many of these ingredients have been researched. These include Senilife® (b), Novifit® (c), and Aktivait® (d).

Senilife® is a supplement containing a unique blend of antioxidants (phosphatidylserine, pyridoxine, gingko extract, resveratrol, and d-α-tocopherol) that work together to help reduce brain-aging behaviors in as little as 7 days according to Ceva Animal Health. Novifit® contains only SAMe tosylate disulfate. Aktivait® contains DHA and eicosapentaenoic acid (EPA), L-carnitine, vitamin C, *N*-acetyl-cysteine, α-lipoic acid, vitamin E, acetyl-L-carnitine, coenzyme Q10, and phosphatidylserine.

Cannabis and AD and CCD

According to Kogan and colleagues, pet owners that have been using cannabidiol (CBD) and hemp extracts to treat anxiety in their dogs and cats have been pleased with the results and feel this treatment is effective (63). CBD affects both GABA and serotonin receptors and has been shown to have anxiolytic properties (64). A review by Maroon and Bost discussed the neuroprotective benefits of CBD, which include decreasing the production of inflammatory cytokines, influencing microglial cells to return to a ramified state, preserving cerebral circulation during ischemic events, and reducing vascular changes and neuroinflammation (65). CBD has been shown to reverse or prevent the development of cognitive defects in a mouse model of AD (66). Other studies show that a combination of tetrahydrocannabinol (THC) and CBD in a full-spectrum product reduced memory impairment in AD mice. In other murine studies, cannabinoids were found to reduce oxidative stress, microglial activation,

and neuroinflammation; facilitate removal of Aβ plaques and reduce their production; and decrease tau protein aggregation (66). Cannabinoids have been used in humans to reduce the signs of dementia in AD patients. Caregivers report decreased distress, agitation, and aggression and improvement in mood, appetite, and sleep quality in AD patients taking cannabis oil (67). Because CCD is a model for AD, this would suggest that cannabinoids may work in a similar way in canine patients. However, there are no published studies or evidence that cannabinoids such as CBD are effective in CCD, and further investigation is needed to determine its efficacy. Although CBD seems to be the most discussed, other cannabinoids, such as cannabigerol (CBG), cannabidiolic acid (CBDA), and tetrahydrocannabinolic acid (THCA), may play a greater role in neuroprotection. A full-spectrum product containing all the cannabinoids is being researched and may be the most successful in treating canine patients (e).

Cognitive Enrichment and Physical Therapy

Regular exercise, social interaction, new toys, and increased stimulation have been shown to improve cognitive dysfunction in older dogs (10, 16, 17, 68, 69). Socialization classes for older dogs that include basic obedience, scent discrimination tasks, and obstacle courses target balance, proprioception, and cognitive skills (68, 69). Owners can be taught to challenge their dogs at home with hide-and-seek games, puzzle toys, and other physical interactions to work on mental stimulation as a preventive and a therapy for CCD (10, 17, 69).

Physical activity might be a useful strategy in therapeutic management by delaying loss of neuromusculoskeletal functioning and the usual complications of dementia. Regular exercise should be promoted by veterinarians for all dogs, especially those that are aged (68-70). There is an inverse relationship between physical activity and Aß protein deposits in the brains of mice (71). If this is also true of dogs, exercise becomes even more critical for dogs showing early signs of CCD. Specialized exercise programs can be designed to safely exercise dogs after individual physiotherapy assessments are completed and other orthopedic, neurological, or medical problems are taken into account (68, 69). Swimming or underwater treadmill walking, for example, could be great modes of exercise that do not impart the same concussive forces on potentially arthritic joints of older animals (68-70).

Chinese Herbs and Acupuncture

In Traditional Chinese Veterinary Medicine (TCVM), CCD is manifested by the loss of *Shen*. An animal with a healthy *Shen* will be alert, responsive to the environment, and exhibit normal behavior. When the *Shen* is lost, the results are poor memory, disorientation, confusion, anxiety, and hyperactivity. According to Xie, 2 common TCVM patterns with similar clinical signs have emerged in CCD:

1. Phlegm Misting the Mind with Heart and Spleen Qi Deficiency
2. Heart Yin and Blood Deficiency along with Brain Blood Stasis (72)

Although clinical signs of the 2 syndromes are similar, a patient with the first syndrome has a pale, wet tongue and deep pulse that is weaker on the right side. A patient with the second syndrome has a dry red or pale tongue and deep pulse that is weaker on the left side (72).

A third pattern, which is also seen in patients with AD and in many dogs with CCD, is one of Kidney Qi and Essence Deficiency leading to Kidney Yin and later Kidney Yang Deficiency (73). Maciocia states that the Marrow is transformation of the *Jing* from Kidneys, and it impacts the brain, spinal cord, and bone marrow; the brain is called the Sea of Marrow, and when it is full, the brain is healthy, but when there is a deficiency, signs of dementia may occur (74).

TCVM would treat these syndromes with herbal formulas, food therapy, and acupuncture. Treatments can be extensive, but most will focus on treating Phlegm, Blood Stasis, and supporting the Kidney. **Table 1** summarizes common veterinary formulas used for treating CCD in dogs depending on the TCVM pattern. **Table 2** lists Chinese formulas used in AD, and **Table 3** lists Chinese food therapy that could be considered for dogs with CCD. (See Tables on pp. 18-19.)

Some combination formulas, such as *Liu Wei Di Huang* (**Table 1**), have been used for treatment of AD as well. *Sai Luo Tong* formula, not a commonly used veterinary formula, consists of the bioactive components extracted from ginseng (*Panax ginseng*), ginkgo, and saffron (*Crocus sativa*) and has been shown to cause significant improvement in neurocognitive function, learning, and memory in AD patients (2, 75). Other Chinese herbal formulas that have been researched for use in AD, such as *Ba Wei Di Huang Wan* (**Table 1**), *Fu Fang Dan Shen,* and *Yi Gan San* (**Table 2**), have also shown encouraging data on treating cognitive and psychological symptoms in patients with dementia (1, 76).

Acupuncture, particularly electroacupuncture, may be beneficial in treating patients with CCD. It should be performed once weekly for 3 to 5 treatments, and then the treatments may be spaced out according to need. In this author's experience, treatments may last 1 to 4 weeks depending on the severity of the dysfunction (72).

Table 1: Common Veterinary Formulas Used for Treating CCD

TCVM Formula	Ingredients	Classical Antecedent	TCVM Pattern Treated	Action of Formula
Stasis in the Mansion of the Mind (e)	Angelica (*Bai Zhi*) Pinellia (*Ban Xia*) Ligusticum (*Chuan Xiong*) Salvia (*Dan Shen*) Ligusticum (*Gao Ben*) Pueraria (*Ge Gen*) Carthamus (*Hong Hua*) Bombyx (*Jiang Can*) Scorpion (*Quan Xie*) Cimcifuga (*Sheng Ma*) Fritillaria (*Zhe Bei Mu*)	*Nao Yu Fang*	Phlegm Misting the Mind, with Heart and Spleen Qi Deficiency	Moves Blood to break down Stasis in the brain and transforms Phlegm
Shen Calmer (e)	Paeonia (*Bai Shao Yao*) Biota (*Bai Zi Ren*) Bupleurum (*Chai Hu*) Salvia (*Dan Shen*) Angelica (*Dan Gui*) Poria (*Fu Shen*) Ophiopogon (*Mai Men Dong*) Ostrea (*Mu Li*) Citrus (*Qing Pi*) Zizyphus (*Suan Zao Ren*) Asparagus (*Tian Men Dong*) Schisandra (*Wu Wei Zi*) Cyperus (*Xiang Fu*) Scrophularia (*Xuan Shen*) Polygonum (*Ye Jiao Teng*) Polygala (*Yuan Zhi*)	*Tian Wang Bu Xin Dan*	Heart Yin and Blood Deficiency with Brain Blood Stagnation	Nourishes Heart Yin and Blood, calms *Shen*, and soothes Liver Qi
Jin Gui Shen Qi Wan (Rehmannia Eight)*	Rehmannia root (*Sheng Di Huang*) Chinese yam (*Shan Yao*) Cornus fruit (*Shan Zu Yu*) Poria (*Fu Ling*) Alisma tuber (*Ze Xie*) Moutan bark (*Mu Dan Pi*) Cinnamon twig (*Gui Zhi*) Prepared aconite (*Fu Zhi*)	*Bai Wei Di Huang Wan*	Kidney Qi Deficiency, Dampness Accumulation	Tonifies Kidney Qi
Liu Jun Zi Tang (Six Gentlemen)	Ginseng root (*Ren Shen*) White atractylodes (*Bai Zhu*) Poria (*Fu Ling*) Pinellia rhizome (*Fa Ban Xia*) Jujube fruit (*Da Zao*) Tangerine peel (*Chen Pi*) Licorice root processed (*Gan Cao Mi*) Fresh ginger root rhizome (*Sheng Jiang*)	*Liu Jun Zi Tang*	Phlegm Misting the Mind, with Heart and Spleen Qi Deficiency	Tonifies Spleen Qi, transforms Dampness, expels Phlegm, and descends Stomach Qi
San Piao Xiao San (Mantis Egg-Case Combination)**, ***	Mantis egg casing (*Sang Piao Xiao*) Fossilized bone (*Long Gu*) Panax ginseng root (*Ren Shen*) Poria (*Fu Ling*) Acorus (*Shi Chang Pu*) Polygala (*Yuan Zhi*) Turtle shell (*Gui Ban*) Chinese angelica (*Dang Gui Shen*)	*San Piao Xiao San*	Kidney Qi Deficiency and Heart Qi Deficiency	Tonifies Heart and Kidney Qi and stabilizes Jing
*Liu Wei Di Huang****	Rehmannia root (*Shu Di Huang*) Cornus fruit (*Shan Zhu Yu*) Chinese yam (*Shan Yao*) Water plantain rhizome (*Ze Xie*) Poria (*Fu Ling*) Tree peony bark (*Mu Dan Pi*)	*Liu Wei Di Huang*	Kidney Qi and Yin Deficiency and Heart Yin Deficiency	Tonifies Kidney Yin Deficiency and Heart Yin Deficiency

*Used in humans for AD as well.

**Turtle shell is replaced with oyster shell by most manufacturers.

***Used for AD.

Abbreviations: AD, Alzheimer's disease; CCD, canine cognitive dysfunction; TCVM, Traditional Chinese Veterinary Medicine.

Effective acupuncture points have included Yin Tang, LI20, GV20, GV14, ST36, HT7, PC6, CV6, CV12, CV17, SP10, LI4, and LIV3 (1, 72).

Table 4 summarizes treatments for CCD.

Summary

CCD is a common neurogenerative disease of aged dogs akin to canine dementia and is considered to be the canine analogue of human AD. It is important for veterinarians to recognize that CCD is not a part of normal aging, and the processes that lead to symptoms of CCD begin much earlier in life. For this reason, veterinarians should consider preventive measures when the dogs are middle-aged to ward off clinical signs and the effects of progressive cognitive decline. Proactively, clinicians could use the DISHAA tool on all canine patients that are 6 years of age and older. Diagnosis of CCD relies on a high index of suspicion by veterinarians and asking the right questions. Therapeutic interventions include dietary modification, nutraceuticals, physical therapy, and cognitive enrichment. Acupuncture and herbal therapy also have a place in the treatment of this complex disease. The key to successful treatment of CCD is multimodal therapy.

Table 2: Constituents of Chinese Herbal Formulas Used in AD

Formula Name	Ingredients
Fu Fang Dan Shen	Chinese salvia root (*Dan Shen*) Notoginseng root (*San Qi*) Oriental sweet gum resin (*Shu He Xiang*)
Yi Gan San	Atractylodes (*Chao Bai Zhu*) Poria (*Fu Ling*) Angelica (*Dang Gui*) Sichuan lovage (*Chuan Xiong*) Cat's claw (*Gou Teng*) Bupleurum (*Chai Hu*) Licorice (*Gan Cao*)

Table 3: Common Foods Used for Chinese Food Therapy for AD and CCD (74)

Condition/Organ Treated	Recommended Foods
Nourish Yin	Black mushrooms, pears, lotus root, carrots, peas, bamboo shoots, lean pork or fish
Tonify Yang	Lamb, goat, deer, ginger, soybeans, pumpkin, broad beans
Resolve Phlegm	Celery, spinach, coriander, bok choy, Chinese cabbage, green leafy vegetables; reduce grains
Weak or Emaciated	Bone broth, chicken soup, eggs, fish
Heart	Vegetables, fruit, asparagus
Spleen	Lean beef, brown rice; avoid greasy, cold, or sour foods
Kidney	Soybeans, pork; avoid pungent foods and excess sweets

Table 4: Summary of Treatments for CCD

	Diet	Drugs	Nutraceuticals	Exercise/Mental Stimulation	Herbs	Acupuncture
Mild cognitive dysfunction	Homemade with MCT or commercial preparation; calorie restriction; veggies and fruits	Selegiline	Fish oil and antioxidants; melatonin; B vitamins; apoaequorin; Senilife®, Novofit®, or Aktivait®	½ hour of walking and swimming, followed by ½ hour of interactive play, puzzles, and brushing and combing	Gingko; green tea (*Camellia sinensis*); turmeric (*Curcuma longa*); Rehmannia 6; full-spectrum CBD	Weekly for 3-5 treatments and then weekly or prn
Moderate to severe cognitive dysfunction	Homemade with MCT or commercial diet; calorie restriction; veggies and fruits	Selegiline; SSRIs; other drugs as needed for sleep-wake cycle, aggression, or other clinical signs	Fish oil and antioxidants; melatonin; B vitamins; apoaequorin; SAMe; Senilife®, Novofit®, or Aktivait®	½ hour of walking and swimming, followed by ½ hour of interactive play, puzzles, nose work, and brushing and combing	Chinese herbs depending on pattern; gingko; green tea; turmeric; full-spectrum CBD	Weekly to every other week

Abbreviations: CBD, cannabidiol; MCT, medium-chain triglyceride; SAMe, *S*-adenosyl-L-methionine.

Endnotes

a. Personal communication by email with Curtis W. Dewey, DVM, MS, Associate Professor, Section of Neurology, Cornell University College of Veterinary Medicine, Ithaca, NY, April 7, 2021

b. Senilife®, Ceva Animal Health, Lenexa, KS 66215

c. Novifit®, Virbac Corporation, Fort Worth, TX 76137

d. Aktivait®, VetPlus Global LTD Animal House, Lytham St Annes, Lancashire, United Kingdom

e. Personal communication by email with Joseph J. Wakshlag, DVM, PhD, Chief Veterinary Medical Officer, Ellevet Sciences, South Portland, ME, January 6, 2021

f. Dr. Xie's Jing Tang Herbal Inc., Ocala, FL 34482

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