Background

“As the world’s population ages, overall health care has improved, yet the incidence of chronic, progressive neurodegenerative diseases has increased.”

Alzheimer disease (AD) is a progressive neurodegenerative disorder characterized by memory loss and cognitive decline. It is the most common form of dementia and a leading cause of death in people over the age of 65, affecting as many as half of those aged 85 or older. In the US alone, the estimated costs for AD treatment were $305 billion, a figure expected to rise to over $1 trillion as population aging continues.

One significant obstacle in the development of a safe and efficacious AD drug is the lack of translational animal surrogates that accurately reflect the etiology, pathogenesis, and heterogeneity of the ailment in humans. These models are crucial for research studies.
The progressive cognitive decline associated with both canine cognitive decline (CCD) and Alzheimer disease (AD) is classified into several stages.\textsuperscript{5}

<table>
<thead>
<tr>
<th>Stage</th>
<th>AD/Dementia</th>
<th>CCD</th>
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<tbody>
<tr>
<td>Early/Mild</td>
<td>People in the early stage of AD exhibit mild memory loss and have increased difficulty managing involved tasks.</td>
<td>Dogs exhibit increased anxiety, a decrease in interactions, with owners, altered sleep patterns, and frequently forget familiar routes or objects.</td>
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<tr>
<td>Mid/Moderate</td>
<td>There is significant memory loss, disorientation, and changes in behavior and/or personality.</td>
<td>Exhibit increased confusion and disorientation, a reduced response to commands, changes in appetite or elimination, habits, and may forget familiar people or places.</td>
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<tr>
<td>Late/Severe</td>
<td>Patients suffer from a complete loss of cognitive function, are unable to recognize familiar people or objects, and require assistance with activities of daily living.</td>
<td>Demonstrate aimless wandering, restlessness, agitation, vocalization, incontinence, and an inability to recognize familiar people or objects.</td>
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While few research organizations maintain dogs until they reach senior status (typically 6 to 7 years old for large dogs and 10 years old for small breeds),\textsuperscript{6} CCD is present in 28\% of dogs aged 11 to 12 years, with a prevalence that increases to 68\% at 15 to 16 years old.\textsuperscript{7} Companion animals that are kept through old age represent a virtually unlimited global source of canines experiencing CCD. These dogs are cared for by pet owners who almost universally support research engagement and welcome options that might ameliorate the CCD-related decline that is experienced by these animals in their care.

The authors posit in this Currents in One Health article that the similarities between the progressive neurodegenerative, neuropathy, and behavioral signs seen in CCD resemble aspects of AD: disorientation, memory loss, and changes in sleep cycles make them suitable and practical surrogates for human dementia and AD research.

The Challenge

AD is the predominant cause of dementia in older people. Even though the FDA recently approved Leqembi (manufactured by Eisai and Biogen), the first AD drug that has shown clinical benefit, its efficacy is limited, serving only to modestly slow cognitive decline. Moreover, its yearly cost of $26,500 will make it inaccessible for many. There remains a pressing need for the development of more effective and affordable translational research models that can improve efficiency, reduce failure rates, and foster more strategic collaborations. Ultimately, CCD translational research models identified by veterinary practitioners have the potential to significantly reduce the high costs associated with drug development, thereby addressing the problem of prohibitively priced medications.

CCD is common in older dogs and a major determinant of morbidity in companion animals. It mirrors many of the physiological and behavioral changes observed in humans diagnosed with dementia and AD, including disorientation, memory deficits, altered social interactions, disruptions in sleep-wake cycles, changes in activity levels, and pathologies such as brain atrophy (Figure 1). Similarities also exist in neuropathology, specifically with the presence of amyloid-\(\beta\) deposits in both extracellular spaces and around blood vessels (cerebral amyloid angiopathy) and increased phosphorylated tau in the brain.\textsuperscript{8}

Despite the well-recognized similarities between AD and CCD, leveraging these parallels for effective treatments has proved to be challenging. Identifying and assessing the early onset of behavioral alterations is difficult in both humans and dogs. Additionally, achieving consensus of the diagnostic value of neurodegenerative biomarkers remains a significant hurdle.\textsuperscript{9}

Diagnosing CCD

Diagnosing AD in humans involves a comprehensive multidisciplinary approach, including the evaluation of balance, sensory responses, and reflexes as well as patient and family interviews, memory, and cognitive skills.\textsuperscript{10} While a probable diagnosis of AD can be made using a combination of sympotmatology and biomarkers, the confirmation of an AD diagnosis is universally agreed to be postmortem neuropathological verification of specific brain changes, including senile plaques and neurofibrillar tangles.\textsuperscript{11} Similarly, diagnosing CCD is multifaceted and presents unique considerations (Table 2).

In veterinary practice, careful physical and neurological examinations, blood tests, and imaging studies (eg, CT scans or MRI, if available) are essential to exclude other conditions with similar symptoms. Tools like wearable sensors are robust markers for CCD-related changes. Any illnesses with symptoms like CCD must be excluded, including brain tumors, osteoarthritis, and metabolic imbalances. Diagnosis relies primarily on observation of clinical science, summarized by the acronym DISHAA.

A thorough understanding of both CCD and AD is crucial for achieving early diagnosis and effective treatment. The growing convergence of technology and research holds promise for novel analytical strategies that can reshape the landscape of cognitive health for both humans and animals. Veterinarians’ ability to identify initial and elusive behavioral changes linked to CCD is vital for early diagnosis. Wearable sensors with remote reporting offer robust markers for these changes, including alterations in sleep patterns and restlessness.
These data will provide CCD and AD researchers with a quantitative platform for developing new analytical strategies for diagnosis, prevention, and treatment.

**Clinical signs**
Both CCD and AD patients experience pathology that progresses gradually, resulting in cognitive decline and behavioral symptoms that range from mild to severe as the pathology advances. The underlying causes and development of the disease lead to similar cognitive-behavioral changes over time. CCD and AD share pathophysiology, including neurofibrillary tangles, significant hippocampal neuron loss, accumulation of amyloid-β protein, neuroinflammation, and an increase in oxidative stress in the brain. The progressive neurodegeneration leads to the remarkably similar behavioral changes that are key features of both CCD and AD. These include increased anxiety, social withdrawal, loss of learned behaviors, disorientation and confusion, reduced responsiveness, and sleep disturbances.

**Laboratory diagnostics**
In addition to biometric data, laboratory diagnostics for CCD include monitoring for comorbidities with symptoms that could mimic the disease, as well as using assays specific for neurodegeneration. Standard testing includes a routine CBC, chemistry profile, and urinalysis. Blood tests may also include assays for liver enzymes (plasma ALT and AST levels can be slightly elevated in CCD) and thyroid hormones to rule out an underactive thyroid. Commonly used CCD/AD-specialized neurodegeneration assays are available (Supplementary Table S1).

**Diagnostic imaging**
Diagnostic imaging plays a vital role in supporting the diagnosis of CCD and uncovering underlying pathology. Imaging methods are available that collectively offer a comprehensive review of brain structure and function and provide essential insights into the presence and progression of CCD (Supplementary Table S2).

**Histopathology**
The postmortem histopathological examination of CCD can reveal several distinct characteristics, providing insights into the underlying pathology, which can collectively depict the complex pathology in CCD, mirroring certain aspects of human degenerative conditions like AD (Supplementary Figure S1; Supplementary Table S3).

**Evaluating behavior**
Evaluating behavioral changes in dogs, particularly as they relate to CCD, requires careful consideration.

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*Figure 1—* A through D—MRI of a 13-year-old Golden Retriever presented with clinical signs consistent with canine cognitive decline and showing generalized cerebral cortical atrophy. E through H—MRI of an 18-month-old male neutered Golden Retriever–Whippet mix with idiopathic epilepsy. A versus E—Sagittal view of diminished interthalamic adhesion in panel A (yellow arrows). B versus F—Transverse views at the level of interthalamic adhesion. In panel B, notice the diminished interthalamic adhesion heights (yellow brackets), widening of the subarachnoid space (white arrows), and enlarged lateral ventricles (white asterisks). D—The small area of signal void (red arrow) is consistent with a cerebral microbleed. (MRI performed at the Royal Veterinary College, courtesy of Dr. Abbe Crawford, the Royal Veterinary College, University of London, London, England, UK.)
of potential underlying diseases or neurological impairments that may influence behavior. Several tools and concepts help address this challenge (Table 3).

**Quantifying behavior**

The emergence of wearable technology offers novel opportunities for the thorough observation and quantification of behavior in pets with CCD. Veterinarians can now uniquely monitor and address CCD in their patients. The ongoing data collection, analysis, and integration of veterinary exams and owner observations will foster a holistic grasp of CCD’s progression, response to interventions, and eventual outcomes. This inventive strategy holds the promise of transforming CCD research and the creation of tailored one-health therapies, thereby empowering veterinary practitioners to deliver personalized care and enhance the well-being of affected patients (Table 4; Supplementary Figures S2 and S3).

**Current Treatment Options**

Both CCD and AD share progressive deterioration of cognitive function, including memory, attention, and problem-solving abilities. However, the underlying mechanisms leading to cognitive decline in dogs and humans are not identical.
The hallmark pathology of AD is the accumulation of amyloid-β protein in the brain, which forms plaques and disrupts neuronal communication. The pathology of CCD is less understood but has been linked to oxidative stress and inflammation in the brain and the loss of brain cells. Despite the differences, there are several treatment strategies that can be used to manage symptoms and attempt to slow the progression of CCD (Table 5).

Recent studies highlight the role of inflammation and oxidative stress in the development and progression of AD, leading to increased interest in the use of anti-inflammatory agents and antioxidants for patient treatment. Pharmacological interventions for AD include cholinesterase inhibitors, which increase the levels of acetylcholine in the brain, and memantine, which regulates the activity of the N-methyl-D-aspartate receptor, both of which are involved in memory and learning.

These available treatments for AD are limited in their efficacy, providing only symptomatic relief without curing or slowing the progression of AD. There is a pressing need for the development of new therapies that target the underlying amyloid-β and tau protein accumulation pathologies, as well as neuroinflammation.

A Veterinary-Centric One-Health Solution

One-health solutions are designed to identify and address the root causes of health problems rather than to simply alleviate the symptoms. Veterinarians stand out as uniquely qualified one-health specialists, owing to their comprehensive clinical experience and deep understanding of disease expression and treatment strategies across multiple species.
Table 5—Treatment strategies to manage symptoms and slow progression of CCD.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Description</th>
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<tbody>
<tr>
<td>Diet</td>
<td>Hill’s Prescription Diet b/d (Hill’s Pet Nutrition Inc) is a specially</td>
</tr>
<tr>
<td></td>
<td>formulated diet that contains a blend of nutrients that support brain</td>
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<tr>
<td></td>
<td>health, improve cognitive function, and reduce oxidative stress in the</td>
</tr>
<tr>
<td></td>
<td>brain.</td>
</tr>
<tr>
<td>Supplements have shown potential to enhance</td>
<td>Antioxidants (eg, vitamins E and C).</td>
</tr>
<tr>
<td>cognitive function in individuals with CCD</td>
<td>Anti-inflammatory omega-3 fatty acids.</td>
</tr>
<tr>
<td></td>
<td>B vitamins.</td>
</tr>
<tr>
<td></td>
<td>Medium-chain triglycerides.</td>
</tr>
<tr>
<td></td>
<td>Ginkgo biloba.</td>
</tr>
<tr>
<td>Medication</td>
<td>Seleniilne (Anipryl): increases neurotransmitter levels to enhance</td>
</tr>
<tr>
<td></td>
<td>cognitive function.</td>
</tr>
<tr>
<td></td>
<td>S-adenosylmethionine: supports neurotransmitter production.</td>
</tr>
<tr>
<td></td>
<td>Melatonin: regulates sleep-wake cycles.</td>
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<tr>
<td></td>
<td>Nicergoline: increases blood flow to the brain.</td>
</tr>
<tr>
<td>Environmental enrichment and behavior modification</td>
<td>Like AD, mental stimulation and daily exercise have been found</td>
</tr>
<tr>
<td></td>
<td>beneficial for managing cognitive decline.</td>
</tr>
</tbody>
</table>

Upon entering the profession, veterinarians commit to an oath that underscores their responsibility to use their scientific knowledge and skills for the benefit of society through the protection of animal health and welfare, promotion of public health, and advancement of medical knowledge. While clinical practitioners have played limited roles as interdisciplinary leaders in the one-health approach to disease management, they can and should become integral managers, proactive partners, and essential integrative collaborators in the ongoing battle against disease. They are positioned to make substantial contributions to the discovery of innovative treatments and medications that can alleviate pain and suffering, enhancing the quality of life of both pets and their people.

The authors advocate for practice-based clinical studies, emphasizing that engaging the collective expertise of the veterinary community can be instrumental in unraveling the causes of some of the most significant global health challenges. Such an approach leverages the veterinary profession’s unique insights, reflecting its potential to make a significant impact on the health of life on Earth.

A One-Health Approach to CCD and AD: the Dogs Overcoming Geriatric Memory and Aging Study

Veterinary Health Research Centers (VHRC) typifies veterinary practitioner–led innovation in clinical trials. Instead of relying on purpose-bred research animals with artificially induced diseases, VHRC cultivates close relationships with veterinarians treating animals seen in their practices that naturally exhibit these conditions. By harnessing this invaluable expertise and studying these genuine cases, our research not only tackles critical challenges in animal health but also holds one-health implications, providing valuable insights into environmental and human health care.

VHRC’s proposed Dogs Overcoming Geriatric Memory and Aging (DOGMA) Study (www.vhrcenters.com/dogma) is a practice-based translational clinical trial designed to yield broad-reaching benefits. The DOGMA Study represents an innovative and interdisciplinary one-health approach that has the potential to enhance our understanding and treatment of both CCD and human neurodegenerative disorders. Early detection of pathophysiological changes are central to the study objectives because they develop well before behavioral changes become evident. For example, in laboratory Beagles, memory impairment may be detected as early as 5 years of age, well before CCD-associated behavioral changes are generally seen. Therefore, the study will be designed around early intervention and comprehensive tracking that will include presymptomatic biometric and biomarker data collection to establish baseline values that can be compared with any later deviations that may be associated with CCD (Supplementary Figure S3). VHRC has engaged in discussions with interest groups focused on both AD and CCD. For the pioneering DOGMA study, anonymous data from 1,000 healthy mature dogs will be analyzed. Depending on their size, these dogs will be aged either 5 to 7 or 7 to 9 years. Importantly, none will show symptoms of CCD. Fitted with biometric collars (PetPace Inc), these dogs will be monitored through end of life, enabling robust data collection and algorithm development.

A secondary objective will be to identify appropriate candidates with spontaneous, naturally occurring CCD for potential enrollment in clinical drug development studies. With a focus on these aims, the DOGMA study intends to offer a comprehensive view of CCD and its links to AD, from early development to potential treatments, aligning with a broader one-health approach that unites veterinary and human medical perspectives.

DOGMA Study benefits

By identifying and enrolling aging pet dogs diagnosed with CCD during routine wellness exams, its impact will extend to owners, researchers studying dementia and AD, and caregivers of those affected by these disorders. The study will provide insights
into neurodegeneration and influences of environmental and genetic factors, along with any impact the comorbidities might have on CCD’s development. General-practice clinicians and specialists will have the opportunity to contribute their insights and provide valuable data on the potential and efficacy of novel treatments and interventions in patients both with and without comorbidities. These could slow or prevent CCD in pets, paving the way for enhanced quality of life for animals suffering from neurodegenerative diseases and, ultimately, their human counterparts. From the human side of one health, by studying naturally occurring age-related cognitive decline in dogs, researchers can gain essential insights that have the potential to advance our understanding of neurodegenerative disorders in both animals and humans.

DOGMA creates a unique bridge between veterinary and human medical understanding, offering an invaluable opportunity for cross-species comparison. The similarities in neurodegenerative processes observed in dogs with CCD and humans with dementia and AD provide a promising avenue for mutual learning and potential therapeutic discoveries.

This interdisciplinary approach, spearheaded by veterinarians in practices across the country and the world, can lead to the identification of common underlying mechanisms, risk factors, and potential treatments for both animals and humans, thereby enriching our knowledge and improving the quality of life for affected individuals of all species.

Summary

While advances in science and medicine have enabled people and pets to live longer and healthier lives, these achievements have resulted in an increased incidence of chronic conditions associated with advanced age and a dramatic surge in neurodegenerative diseases, such as AD and CCD.

AD drug development research aimed at slowing or stopping the progression of neurodegenerative conditions has been hindered by the lack of suitable research animal surrogates that emulate the natural progression of the disease in people. Veterinarians’ ability to identify patients with early signs of CCD will accelerate research studies and the drug development processes, and they will be the earliest beneficiaries of pioneering medicinal advancements, profoundly improving the health and quality of life for their patients and clients.

A collaborative research effort involving veterinary and medical professionals in the context of one health can result in a better understanding of the underlying mechanisms of CCD and AD, leading to the development of more effective treatments with far-reaching implications for both animals and humans alike.

The proposed DOGMA Study has implications beyond the health and well-being of individuals. This will benefit public health by reducing the burden of caregiving and improving the quality of life for those affected by these conditions.

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**Supplementary Materials**

Supplementary materials are posted online at the journal website: avmajournals.avma.org