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. There are substantial similarities in clinical features between AD and canine cognitive decline (CCD). These shared features include the progression of neurodegeneration, neuropathy, and behavioral changes such as disorientation, memory loss, and disrupted sleep cycles (Table 1). Both conditions exhibit similar etiology, clinical presentation, and histopathology. The shared living environment of companion dogs with CCD and humans offers an advantageous one-health perspective for examination of the influence of environmental factors on disease manifestation. Importantly, due to their pivotal role as first responders in the diagnosis and management of CCD, veterinary practitioners are well positioned to become significant contributors to this interdisciplinary research approach. This is particularly relevant as the animals exhibiting traits similar to AD are commonly first discussed and identified during routine veterinary care visits.
Table 1—The progressive cognitive decline associated with both canine cognitive decline (CCD) and Alzheimer disease (AD) is classified into several stages.5

<table>
<thead>
<tr>
<th>Stage</th>
<th>AD/Dementia</th>
<th>CCD</th>
</tr>
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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>
</tr>
<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>
</tr>
<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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</table>

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),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.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 neurodegeneration, 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 Lemab (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-β deposits in both extracellular spaces and around blood vessels (cerebral amyloid angiopathy) and increased phosphorylated tau in the brain.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.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.10 While a probable diagnosis of AD can be made using a combination of symptomatology and biomarkers, the confirmation of an AD diagnosis is universally agreed to be postmortem neuropathological verification of specific brain changes, including senile plaques and neurofibrillary tangles.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.
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.

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**Table 2—Understanding canine cognitive health: aging, diagnosis, and the future.**

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Consideration</th>
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<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Canine aging varies by size. Larger breeds (e.g., German Shepherd Dogs and Retrievers) are considered senior at 6 to 7 years. Smaller breeds (e.g., Terriers and Dachshunds) live longer and are considered senior by age 10. Cognitive decline risk: a quarter of all dogs develop CCD by 8 years old. This age-related disorder affects cognitive functions in ways that are similar to human dementia.</td>
</tr>
<tr>
<td><strong>Presumptive diagnosis and imaging studies</strong></td>
<td>CCD diagnosis process: rule out medical conditions that might present with clinical signs similar to CCD. Initial diagnosis involves a comprehensive approach including a thorough history, assessment, physical and neurological examinations, blood tests. Cognitive assessment tools: help evaluate cognitive function in the diagnosis of CCD and assessing the effectiveness of potential treatments. Canine Cognitive Decline Rating Scale (CCDR). Environmental factors: noise, air pollution, and stress levels should be considered during diagnosis, as they can impact a dog’s cognitive health and potentially worsen CCD symptoms.</td>
</tr>
<tr>
<td><strong>Subjective challenges</strong></td>
<td>Importance of owner observations: Play a vital role in identifying CCD symptoms but can be subjective and influenced by the owner’s perceptions. Valuable for the diagnostic process but should be supplemented with objective measurements. Role of wearable technology: Advancements in wearable technology offer opportunities for more objective and quantifiable measurements. Can provide data that complement subjective owner observations, aiding in early detection and assessment of CCD.</td>
</tr>
<tr>
<td><strong>Early detection</strong></td>
<td>Challenges in early detection: Many owners are not attuned to the subtle behavioral changes that mark the early stages of CCD. This often leads to late diagnosis when irreversible brain damage might have already occurred. Wearable sensor benefits: Wearable sensors can detect changes in sleep patterns, activity levels, and other behaviors that might be indicative of CCD. Early identification of changes can allow expedient initiation of interventions to slow down or manage the progression of the disorder.</td>
</tr>
<tr>
<td><strong>Excluding other illnesses</strong></td>
<td>Ruling out comorbidities: Crucial to exclude other potential illnesses that could cause similar symptoms. DISHAA (disorientation, altered social interaction, altered sleep wake cycle, house soiling, altered activity levels, anxiety) summarizes observations that help differentiate CCD from other conditions.</td>
</tr>
<tr>
<td><strong>Challenges and opportunities</strong></td>
<td>Challenges in identification: Like early human dementia, recognizing the subtle changes that occur at the onset of CCD can be challenging. Current diagnostic strategies often rely on subjective owner questionnaires. Opportunities for improvement: The gradual progression of CCD and its limitations in current assessments highlight the need for enhanced objectivity and quantifiable measures. Improved tools and methodologies will enable more tailored treatment and effective prevention strategies.</td>
</tr>
<tr>
<td><strong>The path ahead</strong></td>
<td>Slow progression of CCD: CCD tends to progress slowly over time. The gradual nature of the disorder contributes to the difficulty in early detection and diagnosis. Limitations of current assessments: Current diagnostic methods have both merits and limitations. The incorporation of objective and quantifiable measures will provide a more accurate understanding of a dog’s cognitive health, enabling personalized approaches to treatment and prevention.</td>
</tr>
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</table>
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.

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Table 3—Evaluating CCD-associated behavior.

<table>
<thead>
<tr>
<th>Tools and concepts</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Evaluation</td>
<td>Major challenge: differentiating CCD-induced behavior changes from manifestations of other diseases or neurological impairment. Key consideration: is the observed behavior change directly due to CCD or caused by concurrent health issues?</td>
</tr>
<tr>
<td>DISHAA</td>
<td>Conceptual profile: DISHAA outlines primary behavioral changes associated with CCD. Elements: DISHAA.</td>
</tr>
<tr>
<td>CADES</td>
<td>Assessment tool: questionnaire used to evaluate presence and severity of dementia in dogs.* Categories: dogs are classified into 4 categories based on changes in social interaction and spatial orientation. Categories: 0 = No evidence of dementia, 1 = Mild and inconsistent evidence, 2 = Moderate and consistent evidence, 3 = Severe and consistent evidence.</td>
</tr>
</tbody>
</table>

*While the CADES questionnaire is a valuable resource for veterinarians and pet owners alike in understanding and managing canine dementia,* additional research is still needed.

Table 4—Objective determinants of canine behavior.

<table>
<thead>
<tr>
<th>Technology</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensor technology</td>
<td>Monitoring collars: equipped with sensor arrays to track biometric data in an animal’s daily life. Captured data: include pulse rate, temperature, heart rate variability, respiration, activity levels, posture, positioning, location, sleep quality, and health index.</td>
</tr>
<tr>
<td>Data analysis</td>
<td>Algorithms analysis: data are analyzed using algorithms to identify deviations from established routines and compare against historical norms (Supplementary Figure S3). Comprehensive profile: behavior, position, and biometric data combine to create a comprehensive physiological and behavioral profile.</td>
</tr>
<tr>
<td>Continuous monitoring</td>
<td>24/7 data collection: continuous monitoring from mature adult to end of life in older individuals. CCD findings: consistent findings with CCD onset and exclusion of other issues might lead to further research enrollment.</td>
</tr>
<tr>
<td>Identifying CCD behaviors</td>
<td>Monitored behaviors: disorientation, interaction changes, sleep-wake cycle shifts, activity changes, increasing agitation, and anxiety.</td>
</tr>
<tr>
<td>Informing veterinary care</td>
<td>Enhanced care: veterinarians use data for informed decisions, personalized care, and improved quality of life in CCD-affected pets.</td>
</tr>
<tr>
<td>Connecting data</td>
<td>Linking data sources: connecting veterinary exams, owner questionnaires, lab diagnostics, and behavior data for associations and insights.</td>
</tr>
<tr>
<td>Potential impact</td>
<td>Revolutionizing research: wearable technology transforms CCD research and one-health treatment development, enhancing understanding and intervention effectiveness.</td>
</tr>
</tbody>
</table>
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.vhrccenters.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 is 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 through end of life, enabling robust data collection and algorithm development.
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