Which Drugs Are Used to Treat Cognitive Dysfunction Syndrome?

Margaret E. Gruen, DVM, MVPH, PhD, DACVB
North Carolina State University

Cognitive dysfunction syndrome is a chronic, progressive disease with a range of clinical signs, including disorientation, changes in social interactions, alterations in sleep–wake cycles, house soiling (in a previously housetrained pet), and changes in activity and learning.[1] Cognitive dysfunction syndrome is characterized by neuronal loss and neuroaxonal degeneration.[2] The neuroanatomic pathology in dogs and cats shares some characteristics with human Alzheimer's disease,[3,4] specifically β-amyloid accumulation, tau phosphorylation, and neuronal loss in the frontal cortex, cerebellum, and hippocampus.[2,5-7] The most common signs of cognitive dysfunction syndrome in dogs include house soiling and an increase or decrease in social interactions[8]; the most common signs in cats include vocalization and house soiling.[9] Both dogs and cats may show signs of anxiety or fear (eg, agitation), which may be a result of disorientation. These clinical signs, particularly being awake at night, can be detrimental to the human–animal bond. Older dogs and cats should be screened for cognitive dysfunction syndrome at annual visits and pet owners educated about the common signs.

Environmental enrichment, mental stimulation, and diet promote cognitive health as pets age. Therapeutics used to treat cognitive dysfunction syndrome are typically chosen to address clinical signs once they have been detected. There are no approved drugs for prevention of cognitive dysfunction syndrome, and only one drug has been approved for dogs.[10] Use of drugs to provide supportive and complementary care can mitigate signs associated with cognitive dysfunction syndrome. Clinician understanding of the rationale and utility of available drugs is crucial, as is balancing medications, owner expectations, and potential drug interactions.

Drug decisions should be based on clinical presentation, and patients should be monitored for treatment efficacy. It can be useful to prioritize the presenting signs to address those most pressing; for example, anxiety and changes to the sleep–wake cycle are often addressed first.

Selegiline

Selegiline is the only FDA-approved drug for treatment of cognitive dysfunction syndrome. It is only approved for use in dogs, although use in cats has been described.[11] Selegiline is a monoamine oxidase inhibitor (MAOI) that specifically inhibits

MAOI = monoamine oxidase inhibitor

monoamine oxidase-B. Its effects in the CNS include increasing phenylethylamine and slowing metabolism of dopamine (and other monoamine neurotransmitters). Selegiline may also decrease free-radical production and enhance free-radical scavenging.[12] In clinical trials, selegiline was shown to improve sleeping, housetraining, and activity in dogs.[13] It has also been shown to improve spatial memory in older laboratory-housed dogs[14] and have positive effects on learning and attention.[15]

Formulation → Oral

Dose (dogs) → 0.5-1.0 mg/kg q24h (administered in the morning)
Dose (cats; extra-label) → 0.25-1.00 mg/kg q24h (administered in the morning)

Key Points

- Improvement or stabilization of clinical signs may take 6 to 8 weeks.
- If there are no adverse effects, owners should be encouraged to continue administering the medication for 2 months then reassess the dog's status. Adverse effects reported in clinical trials included vomiting, diarrhea, hyperactivity/restlessness, ataxia, and disorientation.[16]
- Concurrent use of selegiline with other MAOIs (eg, amitraz) or serotonergic drugs (eg, selective serotonin reuptake inhibitors, tramadol, trazodone) is contraindicated due to increased risk for serotonin syndrome.

Benzodiazepines

In older humans, benzodiazepines may be associated with postoperative cognitive decline and an increased risk for Alzheimer's disease.[17] However, the disease risk in humans increases with both length of treatment and half-life of the medication,[18] and relevance in animals is unknown. Benzodiazepines may be useful in treating anxiety and agitation associated with cognitive decline in humans and may be helpful in treating this condition in dogs. Although a variety of benzodiazepines are widely available, those with a shorter half-life and no active metabolites are preferred.

Lorazepam

Lorazepam is a generally well tolerated benzodiazepine with no active metabolites. Its elimination half-life in dogs is approximately an hour. Side effects can include lethargy or idiosyncratic increases in activity or vocalization. Lorazepam may be beneficial at night for patients that exhibit night waking.

Formulation → Oral

Dose (dogs) → 0.025-0.200 mg/kg up to q8h
Dose (cats) → 0.025-0.050 mg/kg q8-12h

MAOI = monoamine oxidase inhibitor

Nutraceuticals

Various nutraceuticals have been used to treat cognitive dysfunction syndrome. The following discussion is limited to those that have been studied in dogs or cats.

α-Casozepine

α-casozepine is a decapeptide derived from α S1-casein in milk. Though the mechanism of action is not completely understood, α-casozepine appears to be structurally similar to γ-aminobutyric acid. It has been studied primarily for efficacy in anxiety paradigms in cats and dogs[19,20]; in dogs, however, it was evaluated for equivalence against selegiline.[20] α-casozepine may be useful in alleviating signs of anxiety that accompany cognitive dysfunction syndrome.

Formulation → Oral

Dose (dogs, cats) → 15 mg/kg PO q24h

Key Point

- α-casozepine has not been evaluated for use in treating cognitive dysfunction syndrome, but it may be useful for treating comorbid anxiety.

Antioxidants & Phospholipids

Oxidative stress appears to have a role in cognitive disorders by causing damage to proteins and lipids in the brain. Vitamins E and B and resveratrol have antioxidant properties and have been incorporated into supplement combinations and diets. Phospholipids (eg, phosphatidylserine) have also been included for their role in cell signaling. Products that contain a mixture of antioxidants and phospholipids (eg, phosphatidylserine) are available. One such product has been evaluated in an open-label trial with a small number ($n = 8$) of dogs with cognitive dysfunction syndrome.[21] Although positive effects were shown on signs of cognitive dysfunction syndrome,[21] results should be followed with a larger, controlled trial. This

product was also shown to improve performance in a memory task in a placebo-controlled study of laboratory beagles.[22] Other supplement combinations are available outside the United States, one of which includes antioxidants, phosphatidylserine, and omega-3 fatty acids and has been shown to improve scores for house soiling, owner recognition, and number of hours awake during the day.[23]

Dose (dogs) → See package insert.

S-Adenosyl-L-Methionine Tosylate

S-adenosyl-L-methionine tosylate may help maintain cell membranes and regulate cellular functions. It has been evaluated for use in treating depression, osteoarthritis, and liver disease.[24] It has also been shown to selectively improve performance on tasks of executive function in laboratory-housed dogs and cats with cognitive dysfunction syndrome.[25] In cats, treatment was most successful in earlier stages of cognitive decline as compared with later stages.[25]

Dose (dogs, cats) → Dose divided by weight class (≤22 lb; 22-44 lb; >44lb)

Apoaequorin

Apoaequorin* is a calcium-binding protein derived from jellyfish. It is believed to have calcium-buffering effects that protect against cell death. When assessed for effects on attention and memory in laboratory-housed dogs, apoaequorin showed favorable results against both placebo and selegiline for select cognitive tasks, particularly selective attention.[26]

Dose (dogs, cats) → See package insert.

Key Points

Apoaequorin has not been evaluated for beneficial effects in cats but is available in a sprinkles formulation.

Drugs Available Outside the United States

Propentofylline

Propentofylline is a xanthine derivative licensed in parts of Europe for the treatment of signs associated with cognitive dysfunction syndrome in dogs. It acts as a phosphodiesterase inhibitor, inhibits the reuptake of adenosine, and decreases the production of free radicals. In a comparison trial, propentofylline did not increase locomotor activity in older dogs.[27]

Formulation → Oral

Dose (dogs, cats) → 3-5 mg/kg PO q12h

Nicergoline

Nicergoline is an ergot alkaloid derivative that acts as an α_1-adrenergic antagonist and enhancer of cholinergic function via acetylcholine release. It is believed to have some neuroprotective and antioxidant activity. In a comparison trial, propentofylline did not increase locomotor activity in older dogs.[27]

Formulation → Oral

Dose (dogs, cats) → 0.25-0.50 mg/kg PO q24h (administered in the morning)

Diets

Two prescription diets have been labeled to support cognitive health in dogs, including:

- Hills Canine b/d (hillsvet.com)
- Purina Pro Plan Veterinary Diets NeuroCare (purina.com)

Hill's Canine b/d contains supplements of antioxidants, mitochondrial cofactors, and omega-3 fatty acids. Aged dogs fed this diet for 6 months showed improved performance (ie, fewer errors) on an oddity discrimination task as compared with aged dogs fed a control diet.[28] Purina Pro Plan Veterinary Diets NeuroCare is supplemented with antioxidants, omega-3 fatty acids, and medium chain triglyceride vegetable oil. This diet was studied in a randomized controlled trial and was shown to improve signs of cognitive dysfunction syndrome in dogs following a 90-day feeding period, relative to baseline.[29] In another study, dogs fed a diet supplemented with arginine, B vitamins, fish oil, and antioxidants performed better in tests of memory and discrimination.[30] These specific diets are available for dogs, whereas supplementation has been incorporated into the diets of senior and geriatric cats. No veterinary diet has been specifically labeled to support cognitive function in cats. However, there is evidence that middle-aged cats fed a diet supplemented with antioxidants, arginine, B vitamins, and fish oil performed better in a series of cognitive tests as compared with cats fed a nonsupplemented control diet.[31]

See next page for references.

*Of note, the commercial product has been placed on indefinite backorder.

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