A Noncomparative Open-Label Study Evaluating the Effect of Selegiline Hydrochloride in a Clinical Setting*

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ABSTRACT

Six hundred forty-one dogs with clinical signs consistent with canine cognitive dysfunction syndrome (CDS) were treated orally with selegiline hydrochloride at 0.5 to 1.0 mg/kg once daily for 60 days. Response to selegiline treatment on days 30 and 60 were similar. On day 60, 77.2% of dogs showed an overall improvement; response to treatment by clinical sign ranged from 67.8% (activity or sleep/wake cycle) to 77.8% (disorientation and interaction with family members). All dogs enrolled in the study were monitored for possible adverse events; diarrhea (4.2%), anorexia (3.6%), and vomiting/salivation (3.4%) were noted most frequently. Results of this study indicate the majority of the dogs with CDS responded to treatment with Anipryl by day 30.

INTRODUCTION

Canine cognitive dysfunction syndrome (CDS) is a recently recognized age-related disorder thought to result from a combination of physical and chemical changes within the brain.[1–6] The underlying pathophysiology is poorly understood, and research is ongoing. β-amyloid has been shown to be neurotoxic and may be one of the causative factors of CDS.[7] β-amyloid deposition in the form of diffuse plaques has been identified within the cerebral cortex and hippocampus of senior dogs and is strongly associated with deficits in discrimination, and reversal and spatial learning.[2,8–10]

Other age-related physical changes in the canine brain include ventricular dilation, alterations in cerebral vasculature that reduce blood flow, decreased number of cells in the cerebrum and cerebellum, fibrosis of the meninges, and degeneration of cerebral and cerebellar white matter with ceroid lipofuscinosis and generalized gliosis.[4,5,11–14] How these factors contribute to the clinical signs of CDS is currently being evaluated.

The chemical changes that occur in the brains of dogs with CDS are less well defined. Several neurotransmitter abnormalities, including an imbalance or depletion of catecholamines, acetylcholine, and serotonin, have been described in humans and other species with neurodegenerative disorders.[15–21] Monoamine oxidase (MAO) subtypes A and B both play a major role in the catabolism of the catecholamines dopamine and norepinephrine and, to a lesser extent, epinephrine and serotonin.[22]

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The predominant subtype associated with dopamine metabolism varies by species but has not been definitively established in dogs.[23] Dopamine metabolism is believed to accelerate in senior dogs because these animals have an increased accumulation of neuromelanin (a by-product of dopamine metabolism) in their brains and because inhibition of MAO-B appears to enhance dopaminergic function.[24–26]

At recommended dosages, selegiline has been shown to be a selective and irreversible MAO inhibitor in dogs, with a greater affinity for the subtype B enzyme active sites compared with type A sites.[23,24] The mechanism of action for selegiline may be through direct or indirect action on catecholamine levels.[23,27] Selegiline is thought to indirectly enhance the effects of dopamine though inhibition of the catabolism of phenylethylamine (PE) by MAO-B. PE is a potential neuromodulator of catecholamine transmission. At normal physiologic levels, PE has little effect on dopamine activity[28]; at pharmacologic levels, however, PE increases the release and decreases the reuptake of dopamine and other monoamines and may have a postsynaptic dopaminergic receptor–stimulating effect.[24,28] In a recent study, selegiline was shown to induce a marked dose-related increase in PE levels within the hypothalamus and caudate of dogs.[24]

Another possible mode of action for selegiline in CDS patients is through antioxidant activity. It has been hypothesized that formation of free radicals may play a role in certain types of dementia in humans.[7,29,30] Traumatic injuries to the brain result in the formation of free radicals and may contribute to dementia pugilistica.[31] Both ischemia and reperfusion injury are known to produce free radicals in the brain and may also contribute to certain types of dementia in humans.[18,29,30] Superoxide dismutase, catalase, and glutathione peroxidase all contribute to reduce free radical formation.[29] Selegiline HCl increases levels of superoxide dismutase and catalase in the striata of dogs, which may decrease free radical formation and subsequent damage to neurons.[32,33]

Selegiline (Anipryl®, Pfizer Animal Health, Exton, PA) was approved by the US FDA in 1998 for the control of clinical signs associated with canine CDS.[34] Although several studies had been conducted to determine the drug's efficacy in treating CDS, two studies were considered to be pivotal by the FDA. The first was a double-blind placebo-controlled study in which 184 dogs received either a negative placebo control or selegiline at 0.2 or 1.0 mg/k once daily for 4 weeks; 160 of these dogs then received selegiline at 1.0 mg/kg once daily for an additional 8 weeks.[34] The second study was an open-label noncomparative study in which 47 dogs received selegiline at 0.5 mg/kg once daily (the dose was increased to 1.0 mg/kg in three dogs) for 3 months.[34]

Separate target animal safety studies were also conducted. Forty dogs (eight per treatment group) received either a negative placebo or selegiline at 1, 2, 3, or 6 mg/kg for 6 months.[34] The long-term safety of selegiline was evaluated in a double-blind placebo-controlled study in which 41 dogs received a placebo control and 41 dogs received selegiline at 1.0 mg/kg for 2 years and 10 weeks.[35] Additional safety data[34] were gathered by reviewing the adverse events reported in the two efficacy studies.[34,35] From the results of all these studies, the FDA concluded that at a dose of 0.5 to 1.0 mg/kg once daily, selegiline was both effective and safe in controlling the clinical signs associated with canine CDS.

Although CDS has a physiologic etiology, it is most easily recognized by characteristic behavioral changes that are not attributable to a general medical condition such as neoplasia, sensory impairment, or organ failure.[6,36,37] Clinical signs in a pet can be so severe that the owner no longer considers the dog to have an

acceptable quality of life. For this study, clinical signs were divided into four categories of behavioral changes: disorientation, decreased interaction with family members, changes in activity and/or sleep–wake cycle, and loss of housetraining.

At present, the diagnosis of CDS in dogs is one of exclusion. In a manner similar to that used to diagnose dementia in humans, the diagnosis of canine CDS is based on documenting specific clinical signs that are unrelated to other disease processes.[6,36] A routine evaluation should include complete medical and behavioral histories and thorough physical and neurologic examinations. Appropriate diagnostic tests to rule out other diseases that may mimic the signs of CDS should be conducted. The minimum diagnostic test should include a complete blood count (CBC), chemistry panel, and urinalysis. The need for additional diagnostic tests should be determined based on the results of these preliminary tests. If no underlying disease is apparent, the dog should be started on selegiline and its response to therapy monitored.

The noncomparative open-label clinical field study described here evaluated the efficacy of selegiline in controlling the clinical signs of CDS in dogs that were diagnosed and treated under routine conditions. The purpose of this study was to further define the role of selegiline as a treatment for controlling clinical signs associated with canine CDS in addition to what had previously been established in the safety and efficacy studies conducted for FDA approval. In the study described here, selegiline was administered at 0.5 to 1.0 mg/kg once daily for 60 days. Response to therapy after 30 and 60 days of treatment are reported.

MATERIALS AND METHODS

Test Sites and Animal Selection

More than 300 veterinary clinics across the US were invited to participate in this study; 236 clinics in 46 states choose to do so. An identical protocol was used at all sites. Six hundred forty-one dogs, 8 years or older of any sex, breed, or weight with clinical signs consistent with CDS were enrolled in the study. All dogs in the study were owned by clients and were regular patients of the participating veterinary clinics.

Pretreatment Evaluation

A pretreatment evaluation was conducted for two reasons. The first was to diagnose any underlying medical condition other than CDS that might account for the observed clinical signs. The pretreatment evaluation included a medical history; physical and neurologic examinations; and collection of blood and urine samples for CBC, chemistry panel, and urinalysis to assess the dog's general health and to rule out other underlying diseases that could mimic the clinical signs of CDS. All blood and urine samples were submitted to a central laboratory (Covance Central Laboratory Services, Indianapolis, IN) for evaluation.

The second reason for conducting pretreatment evaluations was to confirm that all dogs had at least one clinical sign in a minimum of two of the four general categories of signs associated with CDS (disorientation, decreased interactions with family members, changes in activity and/or sleep–wake cycle, and loss of housetraining). Clinical signs of CDS were documented during the pretreatment evaluation by interviewing the owner or primary caregiver about the dog's behavioral history; this information was recorded on the Behavior History Data Capture Form (Figure 1). The form was completed during two separate pretreatment interviews. The first interview was conducted at the initial examination and the second after blood work results had been reviewed. The goal was to identify and docu-

BEHAVIOR HISTORY DATA CAPTURE FORM											FORM 2
Trial Number: D68C-60-98-13					Case Number:						
Y = Yes N = No + = improved 0 = unchanged – = worse											
IF A CLINICAL SIGN IS NOTED AT DAY 30 OR 60 THAT WAS NOT REPORTED AT THE PREVIOUS VISIT, NOTE THE RESPONSE AS – (WORSE).	Pretreatment Evaluation Circle correct response				Day 30 Primary caregiver should be asked to compare dog to initial visit			Day 60 Primary caregiver should be asked to compare dog to Day 30 evaluation		
DISORIENTATION	1st Interview		2nd Interview		Circle correct response			Circle correct response		
Apparent anxiety or confusion; random or aimless wandering; repetitive pacing; staring into space	Y	N	Y	N	+	0	–	+	0	–
Decreased ability to perform previously learned tasks (i.e., stands at hinge side of door or goes to wrong exit door); gets stuck in corners, under or behind furniture; appears to forget reason for going outdoors or signals repeatedly to go in/out without eliminating	Y	N	Y	N	+	0	–	+	0	–
Inappropriate or excessive vocalization	Y	N	Y	N	+	0	–	+	0	–
ACTIVITY AND SLEEP										
Decreased sleep and/or unexplained restlessness during the evening or night	Y	N	Y	N	+	0	–	+	0	–
Increased sleep during the day or in a 24-hour period	Y	N	Y	N	+	0	–	+	0	–
HOUSETRAINING (For dogs previously housetrained)										
Has urinary or fecal accidents in a previously housetrained dog (indicate # of incidents per week)										
Urinates or defecates indoors soon after being outside; maybe in view of owners	Y	N	Y	N	+	0	–	+	0	–
INTERACTION WITH FAMILY MEMBERS										
Less enthusiasm upon greeting and/or no longer greets owners (in dogs that are aware that owners have arrived) and/or decreased frequency of greeting behavior and/or does not recognize familiar people	Y	N	Y	N	+	0	–	+	0	–

Figure 1. *Behavior history data capture form.*

(form continues on next page)

(Figure 1 continued)

Decreased or no response to being petted and/or decreased or no solicitation of petting or play	Y	N	Y	N	+	0	–	+	0	–
Does not respond to known verbal cues or name; decreased responsiveness to stimuli such as doorbell ringing, sound of can opener	Y	N	Y	N	+	0	–	+	0	–
VETERINARIAN'S INITIALS										
DATE INFORMATION COLLECTED (DD/MM/YY)										

ment all clinical signs of CDS before initiating selegiline therapy.

Inclusion/Exclusion Criteria

Investigators were instructed to exclude any dogs that had evidence of underlying disease with signs that mimicked those of CDS. Dogs with evidence of renal disease, osteoarthritis, hypothyroidism, hyperadrenocorticism, or other conditions were included if the investigator determined that the underlying condition was not contributing to the clinical signs attributed to CDS. Dogs with other behavioral disorders, such as aggression or separation anxiety, were excluded, as were dogs receiving behavioral modification drug therapy (e.g., selective serotonin reuptake inhibitors, tricyclic antidepressants, all other antidepressants, anxiolytics, sedatives, anticonvulsants, opioids, lithium, progestins, methylphenidate). In addition, any dog that was being treated concurrently with products containing MAO inhibitors (e.g., amitraz) or products containing ephedrine, hydrocodone, dextroamphetamine, or levamphetamine was excluded from the study, as per the product label. Dogs exhibiting polyuria and/or polydipsia or those receiving phenylpropanolamine for urinary incontinence or prednisone were excluded from the study if one of the animal's CDS signs included loss of housetraining. Dogs with known seizure disorders were excluded. Animals receiving routinely prescribed medications, such as heartworm and/or flea preventative, thyroid supplementation, and nonsteroidal antiinflammatory agents were allowed to participate in the study.

The diagnosis of CDS was made based on appropriate clinical signs and lack of evidence of other underlying disease that could be contributing to those signs. Determination of whether the known medical condition (e.g., hypothyroidism, sensory loss) was contributing to the noted clinical signs was left to the discretion of the investigator and was, in most cases, supported by the response to selegiline treatment.

Dosage of Selegiline and Clinical Evaluation

Selegiline was administered orally at the recommended dosage of 0.5 to 1.0 mg/kg, to the nearest whole tablet, once daily for 60 days. Dogs were evaluated after approximately 30 and 60 days of therapy. Every attempt was made to conduct these reevaluations within 1 week (± 7 days) of the required date. At the day 30 and day 60 evaluations, owners were asked to assess their pet's response to therapy in two ways. First, owners were asked to evaluate the dog's overall response to treatment. Second, owners were asked to evaluate the dog's response in terms of each of the four categories

of signs associated with CDS using the Behavior History Data Capture Form (Figure 1). Although all dogs were reevaluated on day 60, investigators were advised to perform thorough physical and neurologic examinations on animals that did not respond to treatment to identify any other either newly emergent or previously undiagnosed disease condition. All dogs treated with selegiline were observed for the occurrence of possible adverse drug events.

Statistical Analysis

Descriptive statistics were used to analyze the response variables (behavior history by clinical sign). Frequency (and percentage) distributions of clinical signs or behaviors were calculated in terms of improvement, no change, or worsening of signs. Because there was no placebo control group, no hypothesis tests were made on these data, except for clinical sign by age group. Hypothesis tests were performed (Pfizer Animal Health Biometrics and Data Management, Lee's Summit, MO) on two response variables: the overall behavior assessment at day 30 and day 60 with regard to the dog's age, weight group, breed, and sex using the Cochran Mantel Haenszel chi-square statistical test, which blocked for effect of different clinics.

RESULTS

Signalment of Animals Evaluated for Efficacy

Of the 641 dogs enrolled at 236 veterinary clinics, 474 dogs completed the study according to the protocol. Of these, 264 (55.7%) were female and 210 (44.3%) were male. There were 45 (17.0%) intact females and 219 (83.0%) spayed females; 57 (27.0%) males were intact and 153 (73%) were neutered. There were 316 purebred dogs and 158 mixed-breed dogs representing more than 60 breeds. Breeds represented by 10 or more animals included poodle or miniature poodle (34), Labrador retriever (24), cocker spaniel (24), schnauzer or miniature schnauzer (17), Shih Tzu (17), dachshund (15), Yorkshire terrier (12), English springer spaniel (12), Shetland sheepdog (11), and Lhasa Apso (10). Ages ranged from 8 to 19 years, with a mean age of 13.77 years (13.81 years for females and 13.70 years for males). Body weights ranged from 1.0 kg to 64.5 kg, with a mean weight of 15.7 kg. Doses of selegiline ranged from 0.21 mg/kg to 2.48 mg/kg (only one dog received this dose); the average dose was 0.76 mg/kg;

Pretreatment Evaluation

Abnormal findings on the pretreatment physical examination and/or preexisting medical conditions were reported for 376 of the dogs in the study. Animals with known underlying disease were allowed to participate in the study if the investigator determined that the reported conditions did not contribute to the observed clinical signs associated with CDS. The most common physical examination abnormalities/preexisting medical conditions were lenticular sclerosis/cataracts (37.6%), dental disease (30.8%), and orthopedic disorders such as osteoarthritis (25.5%). Other physical examination abnormalities/preexisting medical conditions (noted in fewer than 15% of the dogs) included cutaneous masses, chronic cardiovascular disease, other ocular diseases (e.g., keratoconjunctivitis sicca), dermatologic disorders, hypothyroidism, and respiratory disease. Neurologic abnormalities were noted in 70 cases and included ataxia, paresis or central proprioception deficits (25 [5.3%] of 474 dogs), decreased or loss of hearing (15 [3.2%] of 474 dogs), and decreased or loss of vision (13 [2.7%] of 474 dogs).

Commonly reported concurrent drug therapy (initiated before selegiline administration) included nonsteroidal antiinflammatory drugs

TABLE 1. Summary of Information Collected Using the Pretreatment Behavior History Data Capture Form

	*No. of Dogs with Sign/Total Cases (%) by Age Group**				
Clinical Sign	*Baseline (all age groups)*	*8–10 Yr*	*11–13 Yr*	*14–16 Yr*	*>16 Yr*
Disorientation	457/471 (97.0)	30/34 (88.2)	158/166 (95.2)	229/231 (99.1)	40/40 (100)
Decreased interaction with owners	420/472 (89.0)	28/34 (82.4)	150/167 (89.8)	205/231 (88.7)	37/40 (92.5)
Changes in activity and/or sleep–wake cycle	449/470 (95.5)	34/34 (100)	157/165 (95.2)	219/231 (94.8)	39/40 (97.5)
Loss of housetraining	347/469 (74.0)	25/34 (73.5)	103/164 (62.8)	185/231 (80.0)	34/40 (85.0)

*Total numbers of dogs vary due to recording errors. Although data points are missing for some questions, there was sufficient information for evaluation of the cases.

(22.8%), heartworm preventatives (21.9%), antibiotics (11.8%), antiarthritic neutraceuticals (6.1%), thyroid supplementation (5.7%), topical ophthalmics (4.8%), topical otic preparations (4.4%), flea control products (4.2%), and cardiac medications (3.8%).

Summary of Pretreatment Behavior History

The Behavior History Data Capture Form (Figure 1) was completed (two separate interviews with the owner) before treatment was initiated to document the presence of clinical signs consistent with CDS. This form was also completed on days 30 and 60 of the study to evaluate response to therapy. Four general categories of clinical signs associated with CDS were listed on the Behavior History Data Capture Form: disorientation, decreased interaction with family members, changes in activity and/or sleep–wake cycle, and loss of housetraining. A summary of pretreatment information gathered using the Behavior History Data Capture Form is shown in Table 1 and represents a consolidation of the data collected at two pretreatment behavior history interviews. When the behavioral history was recorded at both pretreatment interviews, the second interview results are reported. For some animals, the behavioral history was collected at the first interview only, which is the information that is reported. The categories of clinical signs noted before treatment were disorientation (97.0%), decreased interaction with family members (89.0%), changes in activity or sleep–wake cycle (95.5%), and loss of housetraining (74.0%).

Dogs were divided into four age groups for the pretreatment evaluation: 8 to 10 years, 11 to 13 years, 14 to 16 years, and older than 16 years. Although not statistically different, distribution of clinical signs by age shows some general trends. Three clinical signs (disorientation, decreased interaction with family, and loss of housetraining) occurred with the greatest incidence in dogs older than 16 years; disorientation was noted in 100% of dogs in this group. Incidence of changes in activity and/or sleep–wake cycle was reported in 100% of dogs 8 to 10 years. Loss of housetraining was the least frequently reported clinical sign for all age groups, ranging from 62.8% to 85.0%.

Overall Response to Treatment

Owners were asked to evaluate the dog's overall response to therapy on days 30 and 60

TABLE 2. Overall Response to Treatment at Days 30 and 60

	Response to Treatment		
Day	*No. (%) Improved*	*No. (%) Unchanged*	*No. (%) Worse*
30 (n = 471)*	378 (80.3)	89 (18.7)	4 (0.8)
60 (n = 474)	366 (77.3)	91 (19.1)	17 (3.6)

*In two cases, the owners were unable to assess response to therapy on day 30 but were able to determine overall response on day 60. For one case, the response on day 60 was unchanged; for the other case, the response on day 60 was improved. The day 30 Behavior History Data Capture Form was completed incorrectly for a third case; this case was reported as improved on day 60.

as improved, unchanged, or worse compared to the pretreatment evaluation.

Day 30

On day 30, 80% of the owners reported an overall improvement in clinical signs, 19% reported that the dog appeared unchanged, and 1% reported that the dog appeared worse (Table 2).

Day 60

On day 60, 77% of the owners reported an overall improvement in clinical signs, 19% reported that the dog appeared unchanged, and 4% reported that the dog appeared worse (Table 2). Overall response to treatment on days 30 and 60 was independent of age, sex, breed, and weight as tested by Cochran Mantel Haenszel chi-squared statistical test.

Response to Treatment by Clinical Sign

Overview

Owners were also asked to evaluate each clinical sign listed on the Behavior History Data Capture Form (Figure 1) as improved, unchanged, or worse compared with the previous evaluation or interview. There were two or three qualifying statements for each of the four general categories of clinical signs listed. The individual qualifying statements for a particular category were consolidated into one response (i.e., improved, unchanged, or worse) for that general category on day 30 and day 60 (Figure 2).

To determine whether an animal was improved, unchanged, or worse for a particular general category, a numeric value was assigned to each qualifying statement for that category. The consolidated score for a general category was the sum of the various qualifying statements for that category. An improvement was noted as +1, an unchanged clinical sign as 0, and a clinical sign that had worsened –1. Clinical signs were not weighted by severity. The number of urinary/fecal accidents per week was grouped by frequency of occurrence as follows: 0, 1 to 5/week, 6 to 10/week, or more than 10/week. A dog was considered improved if the number of occurrences of loss of housetraining per week decreased to a lower frequency group, unchanged if the number of occurrences remained within the same frequency group, and worse if the number of occurrences increased to a higher frequency group.

Day 30

Response to therapy by clinical signs on day 30 was determined by comparing day 30 findings with baseline history responses (Table 3). Dogs with disorientation, decreased interaction, and loss of housetraining had a similar response to treatment (77.5%, 76.4%, and 73.5% reported as improved, respectively). The lowest response was reported for changes

	Day 30 Response	Consolidated Score
DISORIENTATION		
Apparent anxiety or confusion; random or aimless wandering; repetitive pacing; staring into space	Improved = +1	
Decreased ability to perform previously learned tasks (i.e., stands at hinge side of door or goes to wrong exit door); gets stuck in corners, under or behind furniture; appears to forget reason for going outdoors or signals repeatedly to go in/out without eliminating	Unchanged = 0	0 Unchanged
Inappropriate or excessive vocalization	Worse = –1	
ACTIVITY AND SLEEP		
Decreased sleep and/or unexplained restlessness during the evening or night	Improved =+1	+2 Improved
Increased sleep during the day or in a 24-hour period	Improved =+1	
HOUSETRAINING		
Has urinary or fecal accidents in a previously housetrained dog (indicate # of incidents per week)	10x/ week | 5x/ week | Improved =+1	+1 Improved
Urinates or defecates indoors soon after being outside; may be in view of owners	Unchanged = 0	
INTERACTION WITH FAMILY MEMBERS		
Less enthusiasm upon greeting and/or no longer greets owners (in dogs that are aware that owners have arrived) and/or decreased frequency of greeting behavior and/or does not recognize familiar people	Worse = –1	–1 Worse
Decreased or no response to being petted and/or decreased or no solicitation of petting or play	Unchanged = 0	
Does not respond to known verbal cues or name; decreased responsiveness to stimuli such as doorbell ringing, sound of can opener	Unchanged = 0	

Figure 2. *An example of how responses to the individual qualifying statements on the Behavior History Data Capture Form were consolidated into a single response for a particular general category. Overall response to treatment on days 30 and 60 was compared with the pretreatment evaluations and is indicated in Table 2.*

in activity and/or sleep–wake cycle, with 62.5% of the dogs reported as improved.

Day 60

Response to therapy on day 60 by individual clinical signs was compared with the day 30 response. The day 60 response to treatment for all assessable cases was similar to that reported on day 30 and is summarized for each general category of clinical signs (Table 4). Most dogs that showed improvement on day 30 continued to do so on day 60, although some dogs that showed improvement on day 30 did not show additional improvement on day 60. A small number of dogs that showed improvement on day 30 were reported as worse on day

TABLE 3. Day 30 Response to Treatment by Clinical Sign for Cases That Were Reported as Abnormal Before Treatment

Clinical Sign	*No. (%) Improved*	*No. (%) Unchanged*	*No. (%) Worse*
Disorientation (n = 457)	354 (77.5)	86 (18.8)	17 (3.7)
Decreased interaction with family members (n = 420)	321 (76.4)	91 (21.7)	8 (1.9)
Changes in activity and/or sleep–wake cycle (n = 449)	280 (62.4)	156 (34.8)	13 (2.9)
Loss of housetraining (n = 347)	255 (73.5)	72 (20.8)	20 (5.8)

TABLE 4. Improvement by Clinical Sign on Day 60

Clinical Sign	*No. (%) Improved on Day 30 with Continued Improvement on Day 60*	*No. (%) Unchanged on Day 30 but Showing Improvement on Day 60*	*No. (%) Improved on Day 30 with no Additional Improvement on Day 60*	*Total No. (%) Improved from Day 0 to Day 60*
Disorientation (n = 454)	251 (55.3)	30 (6.1)	72 (15.9)	353 (77.8)
Decreased interaction with family members (n = 419)	222 (53.0)	25 (6.0)	79 (18.9)	326 (77.8)
Changes in activity and/or sleep–wake cycle (n = 447)	184 (41.2)	38 (8.5)	81 (18.1)	303 (67.8)
Loss of housetraining (n = 344)	122 (35.5)	28 (8.1)	86 (25.0)	236 (68.6)

60. The greatest degree of improvement (77.8%) was reported for both disorientation and decreased interaction with family members. A lower response to treatment (68.6%) was reported for both loss of housetraining and changes in activity and/or sleep–wake cycle.

By Age Group

Response to treatment by age on day 60 for animals that were noted by owners to have clinical signs before treatment is presented in Table 5. Although not statistically significant, animals in the 8 to 10 years of age group showed the most improvement of all age groups in decreased interaction with family members (89.3%) and changes in activity and/or sleep–wake cycle (79.4%). Animals older than 16 years showed the least amount of improvement for all four categories of signs, however, this finding was not statistically significant.

Improvement of Normal Dogs

A small number of dogs showed improvement in clinical signs that were not reported as being abnormal on the pretreatment evaluations (Table 6). This observation was noted most frequently in the category of decreased interaction with family members. Of the 52 dogs that were reported to have normal interaction with family members before treatment, 19 (36.5%) animals showed improvement on day 30. For a less subjective clinical sign, such as loss of housetraining, the number of animals

TABLE 5. Response to Therapy by Clinical Sign and Age Group on Day 60

Clinical Sign	*No. of Dogs Showing Improvement/No. Reported with Specified Clinical Sign (%) by Age Group**			
	8–10 Yr	*11–13 Yr*	*14–16 Yr*	*>16 Yr*
Disorientation	23/30 (76.7)	127/157 (80.9)	175/227 (77.1)	28/40 (70.0)
Decreased interaction with family members	25/28 (89.3)	121/150 (80.7)	153/204 (75.0)	27/37 (73.0)
Changes in activity or sleep–wake cycle	27/34 (79.4)	106/156 (67.9)	148/218 (67.9)	22/39 (56.4)
Loss of housetraining	18/25 (72.0)	75/103 (72.8)	125/182 (68.7)	18/34 (52.9)

*Total numbers of dogs vary due to recording errors. Although data points are missing for some questions, there was sufficient information for evaluation of the cases.

TABLE 6. Summary of Improvement Noted on Day 30 by Owners of Animals Reported as Normal Before Treatment

Clinical Sign	*No. of Dogs Showing Improvement on Day 30/No. of Dogs Reported as Normal Before Treatment (%)*
Disorientation	2/14 (14.3)
Decreased interaction with family members	19/52 (36.5)
Changes in activity and/or sleep–wake cycle	3/21 (14.3)
Loss of housetraining	4/122 (3.3)

that showed an improvement after treatment despite being reported as normal before treatment is very low (3.3%).

Disposition of Excluded Cases

Selegiline efficacy was evaluated only in dogs that completed 60 days of therapy and followed the study protocol requirements. Of the 641 dogs originally enrolled in the study, 167 were excluded from efficacy analysis for the following reasons:

- **65** (10%) of 641 dogs were removed from efficacy evaluation because of noncompliance to the protocol. Of these, 41 (64%) were removed because of investigator error (failure to follow protocol, incorrect completion of forms [e.g., no date, illegible or missing data]) and 24 (46%) because of owner noncompliance (failure to return for recheck examination during the allotted time, incorrect medication doses given, owner moved). When it was known that the owner failed to return because of lack of response to treatment, the animals were included in the "no improvement prior to 60 days" category.
- **58** (9%) dogs were euthanized or died.
- Treatment was discontinued in **32** dogs (5%) because of adverse events.
- Treatment was discontinued in **12** dogs (2%) because no notable improvement in clinical signs was seen prior to completing 60 days of treatment.

It can be argued that the exclusion of these 102 dogs because of death, euthanasia, adverse events, or lack of improvement before 60 days of treatment skews the results from a practitioner's perspective. When these dogs were included in the efficacy evaluation the overall improvement after 60 days of selegiline therapy was 64%.

Reporting of Possible Adverse Drug Events

In this study, an adverse drug event was defined as any abnormal clinical sign that occurred while the dog was receiving selegiline without regard to causality (i.e., whether the event was directly attributable to drug administration). The cause of possible adverse drug events was difficult to assess in this population of geriatric dogs with signs of CDS because many of the animals had concurrent or newly emergent conditions and/or may have been receiving other medications. The rate of adverse events reported in this study was similar to that seen in previous studies and reported in the Freedom of Information Summary for this product.[3,4] Possible adverse drug events were reported in 186 cases. The most frequently reported clinical signs included diarrhea (4.2%), anorexia (3.6%), and vomiting/salivation (3.4%). Clinical signs noted less frequently included anxiety, restlessness, or hyperactivity (2.2%), dermatologic disorders (2.2%), disorientation (2.0%), hindlimb paresis and ataxia (2.0%), vestibular signs (2.0%), lethargy (1.9%), orthopedic disorders (1.7%), polydipsia (1.7%), and seizures (1.6%). Investigators (case veterinarians) were asked to assess whether the abnormal clinical signs were a direct result of selegiline administration or due to other factors. The investigators did not consider the majority of all other reported adverse events to be drug related.

Forty-nine dogs were euthanized and nine dogs died during the study. An identified unrelated medical condition or preexisting disease was considered to be the reason for death or euthanasia in many of these cases (27 of 641 dogs; 4.2%). Fourteen (2.2%) dogs were euthanized because of a lack of improvement in clinical signs prior to 60 days of treatment. Nine dogs were euthanized because of possible adverse drug events, which investigators assessed as unlikely to be related to selegiline administration. One dog had received routine vaccinations at the same time selegiline was administered and subsequently developed hemolytic anemia that was not responsive to treatment. Because of concurrent vaccine administration, causality was undetermined for this case. No reason for euthanasia or cause of death was reported for seven (12%) dogs.

DISCUSSION

The first description of canine CDS appeared in the human literature where investigators found similarities in the way canine and human brains age.[1–6] It is well accepted that some humans "age better" than others—some individuals retain their cognitive abilities later in life while others fall victim to various forms of dementia, such as Alzheimer's disease. Various investigators have discovered that dogs age in a similar manner. Some dogs, regardless of breed, lose their ability to recognize and interact with their surroundings as they age while other dogs do not.[1,3] A common pathophysiologic finding in both the human and canine aging brain is deposition of β-amyloid plaques.[2,4–6] β-amyloid has been shown to be toxic in cell cultures.[7] Whether β-amyloid deposition is a cause of dementia or a marker of some other underlying pathophysiology is still under investigation, as are a number of other potential causes such as changes in neurotransmitters and free radical formation. A detailed summary is beyond the scope of this article, however, the evidence clearly identifies canine CDS as a syndrome.

The purpose of this study was to evaluate the efficacy of selegiline in a realistic clinical situation, recognizing the limits of diagnostic testing for the majority of practitioners and the financial constraints of most dog owners. The diagnosis of CDS in dogs is currently one of exclusion because no definitive diagnostic test is available. The presence of an underlying disease that could induce some or all of the clinical signs associated with CDS, including other intracranial diseases, hypothyroidism, hepatic encephalopathy, hyperadrenocorticism, and urinary tract infections, must be ruled out. A complete medical history, thorough physical and neurologic examinations, and laboratory tests (including CBC, chemistry panel, urinalysis, and appropriate endocrine tests and liver function tests) as needed, help eliminate a number of potential concurrent diseases. Additional diagnostic tests to rule out intracranial disease (e.g., analysis of cerebrospinal fluid, magnetic resonance imaging, or computed tomography scan) may also be needed. However, these additional diagnostic tests can be cost prohibitive for some owners and a positive response to treatment can confirm the diagnosis after most of the obvious diseases that can mimic the signs of CDS are ruled out.

In this study, the diagnosis of CDS was made based on appropriate clinical signs and lack of evidence of other underlying disease that could be contributing to those signs. If an underlying condition (e.g., hypothyroidism, sensory loss) was identified, the investigator determined whether the condition was contributing to the clinical signs associated with CDS; if the investigator decided that an underlying condition did not contribute to the clinical signs associated with CDS, the animal was allowed to participate in the study. Whether such dogs responded to selegiline treatment determined the accuracy of the assessment to some degree.

The diagnosis of CDS is also based on recognition of certain behavioral changes. However, animals with CDS often appear normal in the examination room and display the abnormal behavior only in the home environment; thus owners are in a better position to recognize behavioral changes in their pet. Asking owners a series of questions (such as those listed in the Behavior History Data Capture Form; Figure 1) is critical to both identify initial clinical signs as well as to determine the response to treatment. Similarly, the Mini-Mental State Examination (MMSE)[38,39] is used to help diagnose Alzheimer's disease in humans. As with other diseases, such as Lyme disease[40] and toxoplasmosis[41] in which there are no definitive diagnostic tests, response to treatment may be the best available diagnostic test.

This study was conducted as a noncomparative open-label study after the US FDA approved selegiline (Anipryl®, Pfizer Animal Health, Exton, PA) for the treatment of CDS. (The Freedom of Information Summary—Supplemental for Anipryl, 1998 provides information concerning the pivotal safety and efficacy studies that were submitted to the FDA.[34]) Noncomparative open-label studies or Phase IV studies, such as the study described here, are commonly conducted after the FDA has approved a pharmaceutical product (human or animal) to demonstrate the benefits of the product when administered in routine situations.[42,43] Phase IV studies can be comparative or noncomparative and provide valuable information about the effect of various treatment modalities on response to treatment and also allow for monitoring of possible adverse events.[42]

The nonblind nature of the protocol and the lack of a placebo control group limit the results of this study. The placebo effect in studies evaluating drugs for which response to therapy is measured by a behavioral change is relatively high, ranging from 28% to 58% in human

studies[44] and 17% to 56% in animal studies.[34,45] In one animal study,[45] the placebo effect on the objective measurement was greater (56%) than the subjective assessment of the owner or veterinarian (38% and 26%, respectively). A recent review of the placebo effect in animal studies listed investigator bias, a conditioned response by the subject, expectancy by the subject, endogenous opioid release, and human contact as possible reasons for a placebo effect.[46]

The placebo effect in this study cannot be assessed. However, the placebo effect seen in a double-blinded placebo-controlled study evaluating the efficacy of selegiline as a treatment for CDS ranged from 17% to 38% after 30 days of treatment.[34] The selegiline-treated group in this study had a higher response than the placebo group for all clinical signs (33% to 66%); the difference between placebo- and selegiline-treated dogs was significant for three clinical signs (changes in activity, changes in sleep–wake cycle, and improvement in loss of housetraining).[34]

An unexpected observation noted in this study was that a small number of dogs initially assessed by their owners as being normal in a particular category of clinical signs before selegiline treatment showed improvement on day 30 and/or day 60. This was noted most frequently for the category of clinical signs defining a decreased interaction with family members. The fact that the owners initially assessed these animals as normal and then reported an improvement could be interpreted in several ways. It is unlikely that the response was due to selegiline's amphetamine metabolites, as this effect is usually seen at a dose three to six times higher than that administered in this study; furthermore, these effects would more likely be reported as possible adverse events (hyperactivity, restlessness) than as improvements in clinical signs.[47] Two more likely explanations are that the improvement in normal animals indicates either a placebo effect or that owners accept some clinical signs of CDS as a part of normal aging. For the later explanation, it is only when animals improve with selegiline administration that owners appreciate that the behavior was actually a clinical sign of CDS.

The clinical signs of CDS were evaluated for age-related trends. The majority of animals in this study were between the ages of 11 and 16 (337 of 474 dogs; 71.1%). Three of the four clinical signs associated with CDS were reported most frequently in the pretreatment evaluations of dogs older than 16 years of age, with 100% showing signs of disorientation, 92.5% reporting decreased interactions, and 85% reporting loss of housetraining. This group also had the lowest response to treatment for all age groups. These data suggest that older animals not only may be more likely to have a higher incidence of CDS-related clinical signs but also may be less likely to respond to therapy.

CONCLUSION

Canine CDS is a recently described disease.[1–6] Factors that contribute to the underlying pathophysiology associated with CDS are not completely understood. It is most likely a multifactorial condition, with a combination of both physical and chemical alterations occurring within the brain. The overall result is decreased function manifesting as behavioral changes.

The criteria for diagnosis in this study were based on positive responses to questions about four general categories of clinical signs in the absence of other disease conditions that could be attributed to the observed signs. Results of this study show that selegiline can control the clinical signs associated with CDS. After 30 days of treatment, 80% of dogs showed overall improvement in the clinical signs of CDS; after 60 days of treatment, 77% were reported as

improved. Although CDS is ultimately a progressive disease, treatment with selegiline offers a therapeutic option for control of clinical signs when there was previously no alternative.

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