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Behavior Problems in Geriatric Pets

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Aging pets often suffer a decline in cognitive function (eg, memory, learning, perception, awareness) likely associated with age-dependent brain alterations. Clinically, cognitive dysfunction may result in various behavioral signs, including disorientation; forgetting of previously learned behaviors, such as house training; alterations in the manner in which the pet interacts with people or other pets; onset of new fears and anxiety; decreased recognition of people, places, or pets; and other signs of deteriorating memory and learning ability [1]. Many medical problems, including other forms of brain pathologic conditions, can contribute to these signs. The practitioner must first determine the cause of the behavioral signs and then determine an appropriate course of treatment, bearing in mind the constraints of the aging process. A diagnosis of cognitive dysfunction syndrome is made once other medical and behavioral causes are ruled out.

Distribution of behavior problems in older pets

The case load of senior pets referred to veterinary behaviorists provides some idea of the most common behavior concerns among the owners of older pets. In one study including 62 dogs aged 9 years or older, the following behavioral problems were exhibited: separation anxiety (29%), aggression toward people (27%), house soiling (23%), excessive vocalization (21%), phobias (19%), waking at night (8%), compulsive or repetitive behaviors (5%), and intraspecies aggression (5%) [2]. A more recent study including 103 dogs older than 7 years of age indicated a similar distribution of behavioral problems but also attributed a substantial number of cases

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(7%) to cognitive dysfunction [3]. The recent inclusion and, possibly, the limited awareness of cognitive dysfunction as a cause of behavioral signs in the senior pet likely have resulted in an underestimation of its prevalence. The primary presenting complaint in 83 senior cats seen at three behavior referral practices (including 25 cases from Dr. Landsberg's referral practice, 33 cases from Dr. Horwitz's referral practice, and 25 cases from a study by Chapman and Voith [4]) was house soiling (inappropriate elimination or marking) in 73% of cases. Intraspecies aggression (10%), aggression to people (6%), excessive vocalization (6%), restlessness (6%), and over-grooming (4%) were the next most common reasons for referral. Although these studies provide some insight into the most serious behavior concerns of the owners of senior pets (ie, those requiring referral to a veterinary behaviorist), these cases may not be representative of the more common and subtle behavior changes of older pets that are not sufficiently serious, dangerous, or intolerable to necessitate referral. In fact, some of the behavioral signs that arise in senior pets may not seem sufficiently significant for the owners to even mention them to their veterinarian.

In a study of 180 dogs from 11 to 16 years of age that had no underlying medical illnesses, owners were asked to report any signs of cognitive dysfunction, including disorientation, altered sleep-wake cycles, decreased responsiveness to stimuli, less interest in interacting with the owners, decreased activity levels, or increased house soiling [5]. Twenty-eight percent and 68% of the owners of 11- to 12-year-old dogs and 15- to 16-year-old dogs reported at least one sign consistent with cognitive dysfunction, respectively. Furthermore, 10% and 36% of the owners of 11- to 12-year-old dogs and 15- to 16-year-old dogs reported signs in two or more categories, respectively. At a follow-up interview 12 to 18 months later, 22% of dogs that did not have any signs of impairment at the first interview developed at least one sign, whereas 48% of dogs that had impairment in one category were likely to have impairment in two or more categories [6]. In a more recent pet owner survey commissioned by Hill's Pet Nutrition, 75% of the owners of dogs aged 7 years and older reported at least one change in behavior consistent with cognitive dysfunction, but only 12% of these owners reported the change to their veterinarian [7].

In a prospective study of aged cats presented to veterinary clinics for routine annual care, 154 owners of cats aged 11 years and older were asked to report any signs of cognitive dysfunction. The questionnaire included questions about alterations or deficits in special orientation, social interactions, responsiveness to stimuli, activity, sleep-wake cycles, anxiety or irritability, and house soiling. Although 43% of the cats showed signs consistent with cognitive decline, 19 of the cats were removed from consideration because of underlying medical conditions that possibly caused the clinical signs. Thus, 35% of cats were determined to have cognitive dysfunction. A greater percentage of the older cats were affected; 50% of 46 cats older than 15 years of age had an average of 2.5 signs per cat compared

with 28% of the 11- to 15-year-old cats with 1.8 signs per affected cat. In 11- to 15-year-old cats, altered social interactions were most commonly reported. By contrast, the most common signs in cats older than 15 years of age were alterations in activity levels, including aimless activity and excessive vocalization during the day [8].

Cognitive dysfunction as a clinical entity in dogs is reported to arise with increasing frequency beginning at the age of 11 years [1,2,5,6]. Recent experimental evidence suggests that a decline in cognitive function may occur much earlier than typically reported in the clinic, likely because of the limited diagnostic measures available currently (ie, owner reports of clinical signs, absence of objective test measures). Although these initial signs may be subtle and relatively innocuous, they may progress to a point where they have a significant impact on the pet's quality of life and the owner's ability to continue to care for the pet. One Australian survey of veterinary practices indicated that 23% of 90 dogs and 9% of 57 cats were euthanized because of senility [9].

Causes of behavior problems in the aging pet

Medical causes

The aging process is associated with progressive and irreversible changes that could affect a pet's behavior. Any painful or uncomfortable condition (eg, arthritis, dental disease) can lead to increased irritability or fear of being handled. If mobility is affected, the pet may become increasingly aggressive or might have more difficulty in accessing its elimination area. Organ failure, tumors, degenerative conditions, immune diseases, endocrinopathies, and sensory decline are more common in the aging pet and can have profound effects on behavior. Any disease of the central nervous system (eg, tumor) or its circulation (eg, anemia, hypertension) also can affect behavior. For example, behavior changes in hypothyroid dogs can range from lethargy to aggression [10], whereas cushingoid dogs may exhibit altered sleep-wake cycles, house soiling, excessive panting, and polyphagia. By contrast, hyperthyroid cats may be more active, irritable, or reactive to stimuli. The effects that medical conditions can have on behavior are presented in Table 1.

Behavioral threshold: combined factors

Senior pets often present with multiple medical conditions, which may result in increased behavioral signs. Multiple medical factors may "push" the pet beyond a threshold to where a behavior problem is exhibited. This might be analogous to dermatology cases in which multiple stimuli may be required before a pet is presented with pruritus. Medical conditions might also "lower" the threshold at which a behavioral problem is exhibited (ie, level of tolerance). For example, a pet that is fearful of children may begin

Table 1
Common medical conditions in older pets and their effects on behavior

System-organ	Examples of behavioral signs/behavioral implications
Neurologic	Diseases directly or indirectly affecting the central nervous system may lead to changes in temperament and mentation; signs might include those consistent with cognitive dysfunction, personality changes, repetitive behavior, or anxiety.
Neoplasia	Signs vary with tumor type
Seizure disorders	Motor or behavioral and/or psychomotor: usually episodic with an aura and/or a postictal episode with normal function between events
Cranial nerve function	Altered response to stimuli
Toxins	Exogenous: higher risk in pets with polyphagia, compulsive chewing or licking (eg, lead, pesticides, illicit drugs), or endogenous (eg, liver or kidney failure)
Circulatory and/or respiratory and/or hematopoietic	Decreased oxygenation to central nervous system leading to signs ranging from cognitive dysfunction to specific signs related to regions involved
Endocrine	Signs related to hormonal effects (eg, excesses of cortisol, thyroxine sex hormones)
Degenerative pathologic findings affecting neurotransmitter function and receptors	Decline in cognitive function, altered mentation and personality changes: altered receptor function and neurotransmission; French authors describe additional brain pathologic findings leading to involutive depression and hyperaggressiveness
Neuromuscular, peripheral neuropathy	Weakness, decreased mobility, house soiling, anxiety, altered responsiveness to stimuli, irritable, and pain-induced aggression
Musculoskeletal	Mobility, irritability, aggression, house soiling, altered responsiveness to stimuli, decreased social interaction, and increased attention seeking; weakness and/or decreased mobility; increased pain, irritability, aggression, and house soiling
Gastrointestinal	
Inflammatory and/or malabsorption	Irritability, house soiling, night waking, appetite, nutritional effects
Constipation	Irritability, house soiling
Dental	Pain-related aggression, decreased interest in food, irritability
Hepatobiliary disease	Potential for toxic effects on central nervous system; hepatic encephalopathy
Endocrine	
Hyperthyroidism (feline)	Irritability, activity, appetite, marking, aggression
Hyperadrenocorticism	Panting, polyphagia, restlessness, waking, altered elimination habits, cognitive dysfunction syndrome signs
Diabetes mellitus	House soiling, irritability, polyphagia, lethargy

Urogenital	
Renal failure	House soiling, irritability, and/or central nervous system signs if uremic
Urinary tract infection and/or urolithiasis, prostate	House soiling, irritability
Testicular tumors	Thecoma: testosterone effects; mark, mount, aggression Sertoli cell: feminizing effects; aggression
Ovarian tumors	Granuloma cell: aggression, estrus signs
Cardiovascular and/or circulatory and/or respiratory and/or hematopoietic	If altered central nervous system tissue perfusion and/or oxygenation: altered mentation or personality, decreased exercise tolerance, decreased activity, signs consistent with cognitive dysfunction syndrome
Dermatologic and/or skin	Increased irritability: mobility (eg, with footpad and/or nail involvement)
Special senses	Altered response to stimuli: less or more reactive; may be more confused, irritable, or anxious or have altered-sleep wake cycle, especially if multiple senses involved
Vision	Decreased response to stimuli: altered sleep-wake cycle; decreased ability to perform previously learned tasks; altered response to people and/or other pets
Hearing	Decreased and/or altered response to stimuli, including owners and/or strangers and/or other pets; perhaps more reactive, sensitive, anxious, or unpredictable
General and/or multiple organ effects	
Pain	Multiple possible causes (eg, dental disease, anal sacculitis, otitis, arthritis, disk disease): may lead to avoidance, aggression, decreased activity, restless behavior, or house soiling
Obesity	Lethargy, less mobile, less active leading to further cognitive decline; obesity can also have an impact on health, well-being, and longevity
Weight loss, muscle wasting	Decreased activity and/or response to stimuli, lethargy, irritability; if polyphagic, could lead to food stealing, possessiveness, night waking, pica, house soiling
Dehydration, decreased response to thirst	Constipation: house soiling, irritability.
Decreased immune competence, neoplasia	Increased susceptibility to infection, immune disease and tumors: signs related to organ system involved
Hypothermia, decreased thermoregulation	Less interactive, lethargy, anxiety, attention seeking, heat seeking, reluctant to go outdoors, altered sleep-wake cycle
Nutritional balance	Although most pet foods provide adequate nutrition for the senior pet, some home-made recipes and even some commercial foods may not address the needs of the senior pet; insufficient digestibility and nutritional imbalances that might not have an impact on the younger pet may be unhealthy for the senior pet; an improved nutritional state might prevent, improve, or slow the decline of many medical conditions

to bite as it becomes uncomfortable, becomes less mobile, or begins to develop visual or auditory decline. Varying degrees of cognitive decline associated with brain aging may also lead to alterations in the manner in which a pet perceives or responds to stimuli. Therefore, the treatment, or partial control, of underlying medical factors may not entirely eliminate the behavioral problem.

Primary behavior problems

Changes in the pet's environment may also contribute to the emergence of behavior problems. Schedule changes, a new member of the household (eg, baby, spouse), a new pet, or environmental modifications (eg, renovations, new household) all may influence a pet's behavior. Furthermore, medical or degenerative changes may cause the pet to be more sensitive or less adaptable to change. As problems emerge, undesirable responses may be rewarded inadvertently. In addition, as owners become increasingly frustrated, they may add to the pet's anxiety, especially if punishment is used to deter the behavior.

Diagnosis and treatment of behavior problems of the senior pet

The diagnosis and treatment of behavior problems are beyond the scope of this article and are well reviewed in many of the veterinary behavior texts available to the practitioner. In fact, many of the behavior problems of older pets may arise from the same causes (and require the same treatment) as those in younger pets. Because the older pet may be more affected by medical problems, including brain aging, and may be more sensitive and less able to adapt to changes and stressors in its environment, we have chosen to focus on some of the diagnostic and treatment considerations that might be specific to the older pet.

Diagnosis

Medical causes and factors

Virtually any medical condition can affect behavior. As age increases, it becomes increasingly important to look at the pet as a whole and to determine the effect of each organ system on the pet's health and behavior. This approach may differ somewhat from the approach taken toward a younger pet with health or behavior problems, where a group of signs are more likely to be attributed to a single medical problem.

Older pets have a declining immune system and are at higher risk for neoplasia and degenerative diseases, including many conditions that can be quite painful, such as arthritis and dental disease. Organ function and the special senses also become increasingly impaired with age. Pain and sensory impairment have profound effects on behavior and may be underreported, especially in cats. In one canine study, owners reported signs attributed to

visual impairment in 41% of 11- to 12-year-old dogs and 68% of 15-to 16-year-old dogs. Owner estimates of hearing impairment ranged from 48% of 11- to 12-year-old dogs to 97% of 15- to 16-year-old dogs [6]. These signs could be caused by impairment of the sensory organ itself or cognitive dysfunction, where sensory transmission and processing are impaired.

Behavior and memory circuits are mainly located in the forebrain, such as in the limbic system and hippocampus. Therefore, a change in personality or mood, inability to recognize or respond appropriately to stimuli, and loss of previously learned behavior might be indicative of any type of forebrain involvement. In some cases (but not all), there may be other concurrent clinical signs, such as cranial nerve involvement, seizures, motor deficits, or emesis. Alterations in consciousness, awareness, and responsiveness to stimuli can arise from any disease process that involves the brain stem or forebrain but may also arise if there are deficits in the sensory system that provides input into these brain areas. Behavioral signs may also be caused by health issues that do not specifically affect the central nervous system or cognitive function. For example, any disease that affects elimination (eg, frequency, volume, control) could lead to house soiling. Some of the common medical conditions in older pets and their effects on behavior are presented in Table 1. For more details on screening the well and sick senior pet, the reader is directed to review the recently published guidelines of the American Animal Hospital Association (AAHA) task force on senior care.

Primary behavior problems

As part of any diagnostic workup, the first step is to determine what medical conditions might be causing or contributing to the behavioral signs and what impact they might have on the treatment of the problem. Therefore, should any behavioral signs or alterations in behavior arise, a physical examination, including a full neurologic assessment, as well as appropriate screening and diagnostic testing is required initially. The behavioral history also is a critical element in diagnosis to ensure that all signs are recognized and all inciting and contributing factors are considered. The history may reveal a significant change in the environment (eg, moving into a new home, change in owner's schedule) or new consequences (eg, particularly fearful event). In addition, some problems may have been present long before the pet became elderly, yet the behavior has only recently become a problem for the owners. For example, the pet that is potentially aggressive to strangers or children might not exhibit problems until a new spouse or child moves into the home. Of course, the older pet might be more sensitive and less able to adapt to changes in its environment.

Treating behavior problems in geriatric pets

The treatment of behavior problems, regardless of age, generally requires a combination of behavior modification as well alterations to the pet's

environment. With the onset of health problems, some of which may be irreversible, it may become increasingly difficult to teach new tasks or to undo the effects of previous learning. Therefore, clear information regarding the prognosis and the limits of what may be achieved needs to be provided to the owner so as to determine what treatment regimen would be most practical and acceptable for the problem(s) at hand.

Aggression to human beings

Aggression in senior pets may arise as a result of medical problems that lead to pain, altered perception, altered recognition of stimuli (eg, sensory decline, cognitive dysfunction), or altered mentation that might arise from diseases affecting the central nervous system (see Table 1). Older pets, whether as a result of cognitive decline or other health issues, may be more irritable, anxious, and fearful, and thus increasingly aggressive toward individuals who are unfamiliar. Pets with pain or sensory decline also may begin to react more fearfully or aggressively toward novel stimuli. In addition, stimuli that were formerly acceptable to the pet may no longer be tolerated (eg, petting, brushing, teeth cleaning, lifting). Therefore, identifying and treating all underlying medical problems might result in improvement (eg, reducing pain). In addition, all stimuli possibly leading to aggression must be identified. Although avoiding potentially aggression-evoking stimuli could be the best and most practical option, the use of a reward-based retraining program may help to eliminate fear and increase desirable responses. Punishment of any type must be avoided. A leash and head halter in dogs (leash and harness in cats) can help to ensure safety and control as well as to improve communication with a pet whose sight or hearing is in decline. Clicker training also can be especially useful for older pets that are not significantly hearing impaired. Desensitization and counterconditioning techniques are needed to resolve anxiety and fear associated with the specific stimuli. Drugs for cognitive dysfunction might be indicated, but antidepressants, such as fluoxetine, and anxiolytics, such as buspirone or benzodiazepines, also could be useful, depending on the cause of the aggression.

Intraspecific aggression

Aggression between dogs in the home may arise as the younger dog matures and the older dog ages. With increasing age, the older pet may begin to respond differently to the younger pet because of cognitive decline, sensory decline, or mobility issues, which, in turn, could lead to anxiety and aggression on the part of the younger pet. Similarly, the senior pet may be unable to recognize or respond to the signals of the younger pet, leading to further anxiety and aggressive interactions. Although desensitization and counterconditioning should be the primary focus of treatment, the age and health of the older pet may limit what can be accomplished. Therefore, increased supervision (perhaps with a leash and harness or a leash and head halter) and environmental alterations that prevent undesirable interactions

may be necessary as well. If cognitive dysfunction is an issue, medical treatment should be useful. Fluoxetine may also be useful for stabilizing mood, whereas anxiolytics could be considered on rare occasions.

House soiling

For house soiling that arises in senior pets, medical issues must first be addressed. Any disease process that increases urine output or frequency can lead to house soiling, especially if the owner cannot change his or her schedule (dogs) or increase the frequency of litter box cleaning and the number of litter boxes (cats) to accommodate the increased need to eliminate. Similarly, bowel diseases that lead to altered frequency or increased discomfort can lead to inappropriate defecation. Close attention to history should help to determine whether marking, incontinence, or cognitive dysfunction is an issue. Another important consideration in the history is whether there is any indication of increased fear or anxiety that could lead to house soiling or increased marking behavior. In addition to treating the underlying medical problem, dogs may require more frequent trips outdoors. If the pet eliminates indoors when the owner is at home, reinforcing of outdoor elimination in addition to increased supervision is required. Environmental alterations, such as confining the pet during departures, allowing for an indoor soiling area, or adding a dog door, may be considered also. For cats, a wide array of environmental modifications, especially with respect to the height and type of litter box, might help to address issues like polyuria or decreased ability to access and use the litter box (eg, arthritis, visual deficits). These can include adding new litter boxes, more frequent litter box cleaning, changing litter type to one with reduced clumping, alterations to the litter box so that it is larger or has lower sides, improving access and lighting to the litter box, or merely preventing access to problem areas. Although Feliway (Veterinary Product Laboratories, Phoenix, AZ) or drug therapy, such as fluoxetine or buspirone, might be useful if there is a marking component, it has little or no effect on litter avoidance and location preferences.

Separation anxiety, fear, and phobias

A change in the pet's daily routine can have a greater impact on the senior pet, which is more sensitive to change and less able to adapt. In addition, medical problems like cognitive dysfunction, sensory decline, organ failure, and endocrinopathies may result in increased fear and anxiety as well as altered responses to stimuli. In turn, the owner's response, whether it is increased frustration and punishment or the use of affection and treats in an attempt to calm the pet down, can further serve to aggravate the problem. Although the prognosis may be poorer for the senior pet with fear and anxiety, some improvement should be possible if underlying medical problems can be controlled at least in part and the owner institutes appropriate behavior modification techniques. Treatment of separation anxiety and noise phobias generally requires the same steps as with the

younger pet. In particular, environmental adjustments to help the pet and owner cope, training relaxation, providing a predictable daily routine, teaching the owner to ensure a calm and settled response before attention or reinforcers are given (learn to earn), and desensitization and counterconditioning to departure stimuli can be used. Head halter control also can help to train and calm fearful or anxious dogs. Drug therapy is often advisable when the pet is fearful, anxious, or phobic, but special attention to the selection, benefits, and risks of pharmacologic intervention is required in the senior pet. Pets with cognitive dysfunction might be treated with selegiline, which should not be combined with antidepressants. Pheromones and some natural compounds, such as melatonin, may be useful for some problems, with little or no chance of adverse effects. Sedating and anticholinergic drugs can have additional risks in the elderly, whereas pets with renal or hepatic compromise require cautious use of drugs excreted by the kidneys or metabolized by the liver, respectively. For example, compared with clomipramine or amitriptyline, fluoxetine is neither sedating nor anticholinergic; buspirone is a nonsedating anxiolytic; and oxazepam, lorazepam, and clonazepam are benzodiazepines that might be considered in pets with hepatic compromise because they have no active intermediate metabolites. Dose information is presented in Table 2.

Excessive vocalization and nocturnal restlessness

Elderly pets are particularly prone to untimely and excessive vocalization as well as to waking at night. Although cognitive dysfunction and medical

Table 2
Drug dosing guidelines

Drug	Dog	Cat
Selegiline	0.5–1.0 mg/kg q 24 hours (mornings)	0.5–1.0 mg/kg q 24 hours (mornings)
Nicergoline	0.25–0.5 mg/kg q 24 hours (mornings)	1.25 mg q 24 hours (mornings)
Propentofylline	3 mg/kg bid	12.5 mg q 24 hours
Oxazepam	0.2–1.0 mg/kg bid	0.2–0.5 mg/kg bid
Lorazepam	0.02–0.1 mg/kg prn	0.02–0.1 mg/kg bid
Clonazepam	0.1–0.5 mg/kg bid–tid	0.1–0.2 mg/kg sid–bid 0.02 mg/kg sid–qid (sleep disorders)
Buspirone	1.0–2.0 mg/kg bid–tid	2.5–5.0 mg per cat bid
Fluoxetine	1.0–2.0 mg/kg q 24 hours	0.5–1 mg/kg q 24 hours
Melatonin	0.1 mg/kg sid–tid	0.5 mg

Abbreviations: bid, twice daily; prn, as needed; q, every; qid, four times daily; sid, once daily; tid, three times daily.

Note that the only products licensed for veterinary use in this table are selegiline for dogs and propentofylline and nicergoline for dogs in some countries outside North America. Therefore, most doses are only based on anecdotal guidelines, and side effects and contraindications are not established for off-label use.

problems may be a cause of night waking or altered sleep-wake cycles, the pet's daily routine and owner responses may also be major contributing factors. Pets that sleep more during the day and have a decrease in daily activity and mental stimulation may be awake and more active through the night. Owner responses may then further aggravate the problem when trying to calm, quiet, or settle the pet by reinforcing the behavior. Conversely, the owner who is frustrated and upset by the pet's behavior and uses punishment to try to settle the pet may further increase the pet's anxiety. In addition to any medical treatment that might be indicated, owners must ensure that they do not reinforce the undesirable responses; they must provide a stimulating daily routine to ensure that the pet regularly rests, naps, and sleeps through the night. This may be difficult because of the pet's decreasing interest and physical ability to engage in daily activities; however, alternatives to running and playing could include short walks; short reward-based training sessions; and a variety of new stimuli, such as manipulation and chew toys. In addition to therapies that help to re-establish normal sleep-wake cycles, such as night time sleep aids, day time stimulants, or antidepressants, drugs and complimentary forms of therapy for cognitive dysfunction might be useful.

Repetitive and compulsive disorders

An increase in restlessness as well as in stereotypic or repetitive behaviors is reported in senior pets. Unless there is an identifiable change in the pet's environment, the onset of these problems in older pets likely is indicative of cognitive dysfunction syndrome or some other underlying medical cause. In addition to medical treatment, treatment for compulsive disorders generally requires that the pet be given a more predictable daily routine with sufficient outlets to keep it occupied (eg, social play, object play) during times it is not resting or sleeping. Because the older pet may be less active and interactive, it can be challenging for the owner to ensure that the pet is provided with sufficient novel and stimulating activities, but the absence of sufficient enrichment may, in fact, compound the problem. Selegiline and dietary therapy should be considered if the signs are consistent with cognitive dysfunction syndrome, but for compulsive disorders, fluoxetine might be the first drug of choice because it is neither sedating nor anticholinergic.

Cognitive dysfunction syndrome

Cognitive dysfunction is a neurodegenerative disorder of senior dogs and cats that is characterized by gradual cognitive decline over a prolonged period (18–24 months or longer) [1,11–13]. Initially, the characterization of cognitive dysfunction was established in the laboratory by comparing the performance of young and elderly dogs on a variety of cognitive tasks using a standardized test box (Fig. 1) [1,14–19]. Similar to human beings, aged

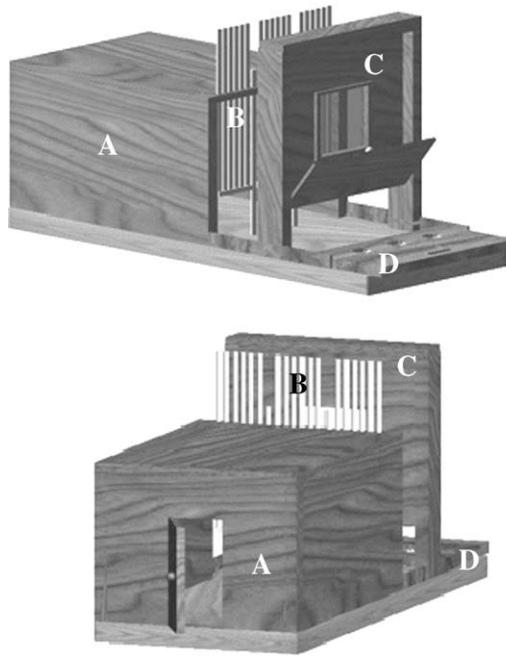

Fig. 1. An illustration of the standardized test apparatus used for canine cognitive testing. The top panel shows the side on which the tester is located, and the bottom panel shows the rear of the apparatus. For the duration of cognitive testing, the dog remains in a wooden chamber (*A*), from which the dog enters through a hinged door in the rear. Adjustable metal bars (*B*) provide an area through which the dog can use its head to access the response area. A wooden partition (*C*) separates the tester from the dog. The tester is able to view the dog at all times through a one-way mirror located in the partition. The tester can present a tray (*D*) to the dog by raising a hinged door on the wooden partition and sliding the tray into the response area. Depending on the cognitive task, various objects may be located over any of the three wells in the tray; the dog is required to displace the correct object to obtain a food reward in the corresponding well. The tester withdraws the tray and closes the hinged door between trials or during delays. (Courtesy of J. Costa, Toronto, Ontario, Canada.)

dogs typically do not demonstrate decline in simple learning, such as when they are repetitively rewarded for approaching one of two distinct objects [20,21]. After a dog learns this simple discrimination task, the reward contingencies are reversed so that the previously rewarded object is no longer rewarded and the dog must learn to respond selectively to the object that was not rewarded in the simple learning task (Fig. 2). When this reversal phase is implemented, aged dogs require significantly more attempts to learn to respond consistently to the rewarded object than young dogs [14,20]. This impairment might be analogous to executive function impairments observed in human aging and Alzheimer's disease [14]. Spatial memory also can be examined by assessing a subject's ability to recall the location of a food reward after a delay of 5 seconds or more (Fig. 3);

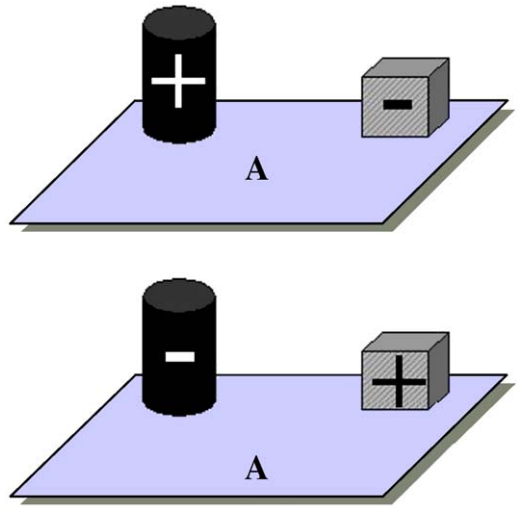

Fig. 2. An example of an object discrimination task. The dog is presented with one of two objects on the sliding tray (*A*; see Fig. 1). As an example of a simple learning task (*upper panel*), the dog would be rewarded for responding to the cylinder (+) but not for responding to the cube (−). Once the dog selectively responds to the cylinder, it then can be tested on a reversal learning task (seen in the lower panel). For the reversal learning task, the dog must modify its response pattern and selectively respond to the cube (+) but not to the cylinder (−). During both tests, the location of the objects is randomized between trials and an unobtainable food reward is presented with the nonrewarded object to prevent the use of olfactory-based responses.

subsequently, the dog's memory can be taxed to a greater extent by increasing the delay [17,19]. Using memory tasks, old dogs can be separated into three groups (unimpaired, impaired, and severely impaired), which may correspond to the three human subgroups of successful aging, mild cognitive impairment (MCI), and dementia [17,21]. Although the age of onset may be 11 years or greater before clinical signs become apparent in dogs, recent findings suggest that cognitive decline can be detected as early as 6 years of age in the laboratory environment. In particular, spatial memory ability declines early in dogs (Fig. 4) [22,23]. Thus, many parallels are observed between canine cognitive aging and human aging and Alzheimer's disease. Specifically, the disease process can be detected long before clinical signs appear using sophisticated cognitive testing procedures, and spatial memory and executive function are impaired early in the disease process.

To determine whether a dog or cat might be showing signs of cognitive dysfunction, veterinarians must rely almost entirely on owner-reported history. Only with careful questioning is it likely that signs would be detectable in the earliest stages of development. By contrast, subtle changes might be more noticeable in animals that have had a high level of training (eg, agility training, service work).

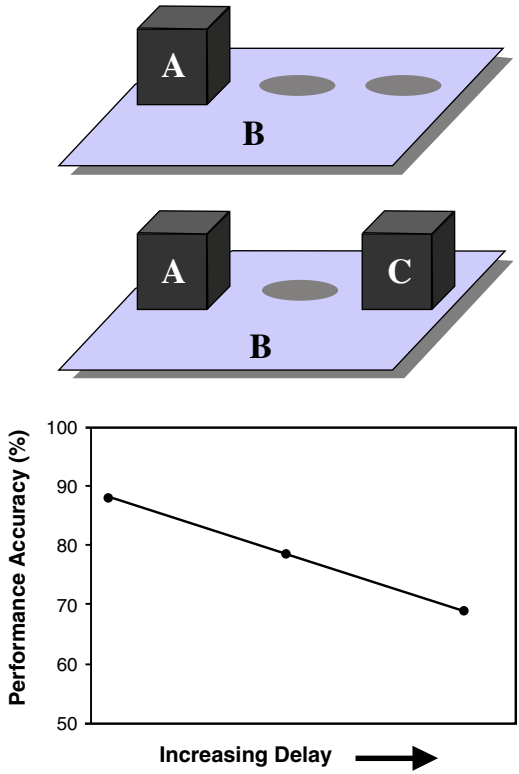

Fig. 3. A schematic of the spatial memory task. During the initial phase (*upper panel*), the dog is presented with an object (*A*) on the sliding tray (*B*; see Fig. 1). After the dog displaces the object and obtains the food reward in the well beneath the object, the tray is withdrawn for a delay. After the delay (*middle panel*), the dog is presented with two objects identical to that in the initial phase; one object is in the same location as the initial phase, and the other is located over one of the remaining two food wells. The dog is rewarded for responding to the object in the novel location (in this case, object *C*). For all spatial memory testing, the locations of the objects are randomized between trials and an unobtainable food reward is presented with the nonrewarded object to prevent the use of olfactory-based responses. The lower panel shows a representative graph of the data obtained using this task; as the delay increases, performance accuracy decreases.

Cognitive dysfunction may cause behavioral changes in the following categories:

1. Spatial disorientation and/or confusion
2. Altered learning and memory (eg, house soiling, learned commands, trained tasks)
3. Activity: purposeless, repetitive, or decreased
4. Altered social relationships
5. Altered sleep-wake cycles (eg, night waking)

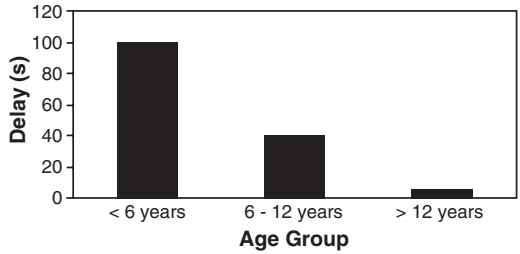

Fig. 4. Representative data of maximal memory across age groups on a spatial memory task. The maximal memory is the longest delay a dog can perform at successfully when tested using an incremental delay procedure over a given number of days (typically 40 days). Dogs younger than 6 years of age can perform successfully at much longer delays (eg, 100 seconds) than dogs older than 6 years of age (eg, 40 seconds). Many dogs older than 12 years of age cannot perform at extremely short delays (eg, 5 seconds).

6. Increased anxiety or restlessness
7. Altered appetite and/or self-hygiene
8. Decreased perception and/or responsiveness

Diagnosis

The history, physical, and neurologic examinations, along with the results of screening tests, lead to a diagnosis or determine if further tests are indicated (eg, radiographs, ultrasound, MRI, brain stem auditory evoked response [BAER]). Ensuring that the owner has provided a complete list of all presenting signs (behavioral and medical), including any behavioral changes in comparison to when the pet was younger (<7 years), provides a framework for determining what medical problems might be responsible for the signs. The findings of the physical examination, previous health problems, and concurrent medication help to guide the practitioner toward what diagnostic tests are initially necessary. The results of these initial tests may then necessitate further diagnostics (eg, radiographs, ultrasound, MRI, BAER) or a therapeutic treatment trial (eg, pain management medication) to achieve a more accurate diagnosis and to determine if the clinical signs resolve. Ruling out all other possible medical conditions that may cause or contribute to the presenting signs leads to a diagnosis of cognitive dysfunction.

Aging and its effect on the brain

A number of anatomic changes can be identified in older dogs and cats; however, it is unclear which of the changes are responsible for which signs. With increasing age, there is a reduction in brain mass, including cerebral and basal ganglia atrophy; an increase in ventricular size, meningeal calcification, demyelination, and glial changes (including an increase in the size and number

of astrocytes); increasing amounts of lipofuscin and apoptic bodies; neuroaxonal degeneration; and a reduction in neurons [24,25]. There is also an increased accumulation of diffuse β-amyloid plaques and perivascular infiltrates in dogs, cats, and human beings with cognitive dysfunction (Fig. 5). In dogs and cats, the plaques are diffuse and lack a central core, although in Alzheimer's disease, the amyloid distribution includes neuritic plaques and concurrent neurofibrillary tangles [12,13]. No clear evidence for early tangle formation has been found in aged dogs, although there may be evidence of early neurofibrillary tangle formation in cats [26].

Numerous vascular and perivascular changes have been identified in older dogs, including microhemorrhage or infarcts in periventricular vessels. Arteriosclerosis of the nonlipid variety may also be seen in the older dog or cat (as a result of fibrosis of vessel walls, endothelial proliferation, mineralization, and β-amyloid deposition). This angiopathy may compromise blood flow and glucose use. Functional changes that may occur in the aging brain include depletion of catecholamine neurotransmitters, an increase in monoamine oxidase B (MAOB) activity, and a decline in cholinergic integrity [27–29]. Cholinergic decline is well established in human aging and Alzheimer's disease [30] and may play a significant role in the early spatial memory decline observed in dogs [31].

Role of β-amyloid in cognitive decline

β-Amyloid is undetectable in young dogs and cats but is extensive in the oldest dogs and cats. Although the exact role of β-amyloid accumulation in the development of cognitive dysfunction is yet to be determined, it is neurotoxic and can lead to compromised neuronal function, degeneration of synapses, cell loss, and depletion of neurotransmitters and is correlated with the severity of cognitive dysfunction [13,32]. In dogs, errors in learning tests, including discrimination, reversal, and spatial learning, were strongly associated with increased amounts of β-amyloid deposition, indicating a correlation between cognitive dysfunction and β-amyloid accumulation, but a causative role has not been established [33].

Role of reactive oxygen species in cognitive decline

A small amount of oxygen that is used by the mitochondria for normal aerobic energy production is converted to reactive oxygen species (also known as free radicals), such as hydrogen peroxide, superoxide, and nitric oxide within the mitochondria. As mitochondria age, they become less efficient and produce relatively more free radicals and less energy compared with younger mitochondria [34,35]. Increased monoamine oxidase (MAO) activity may also result in increased liberation of oxygen free radicals. Normally, antioxidant defenses, including enzymes like superoxide dismutase (SOD), catalase, glutathione peroxidase and free radical scavengers like vitamins A, C, and E, eliminate free radicals. If the balance of detoxification and production is tipped in favor of overproduction, as is the

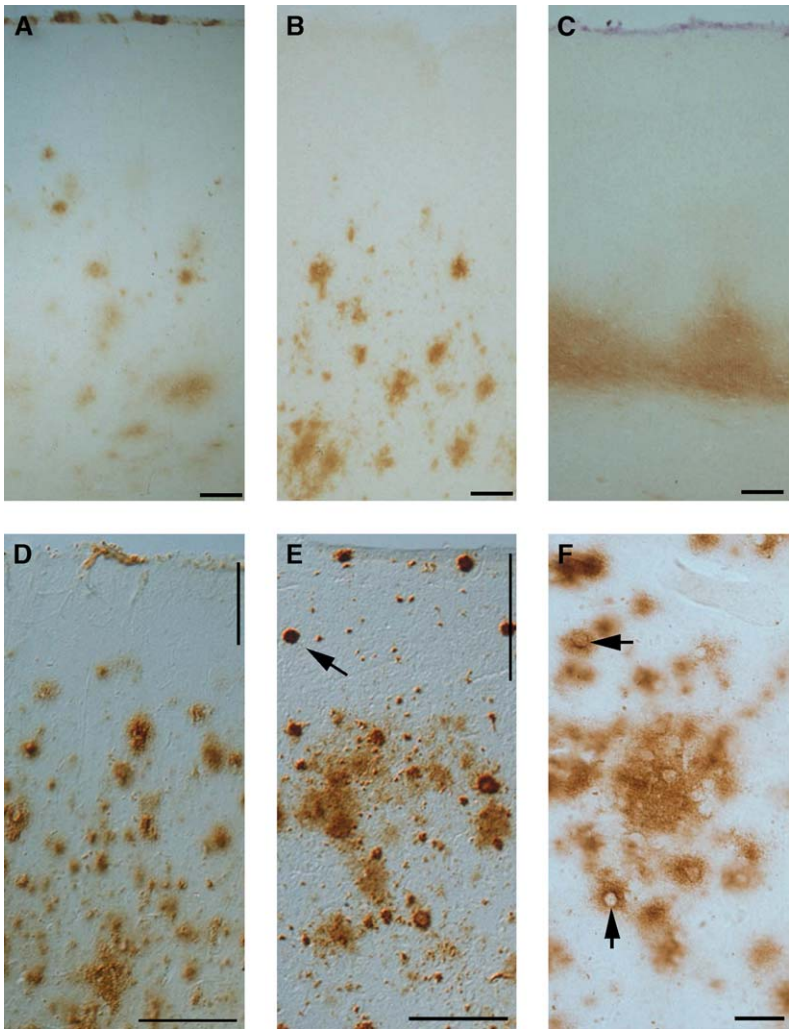

Fig. 5. (*A*) β-Amyloid immunostaining in the prefrontal cortex of a 13-year-old Beagle dog demonstrates diffuse β-amyloid plaques in layers III to VI. (*B*) A section from the frontal cortex of a nondemented 90-year-old woman illustrates a similar pattern of plaque deposition as that seen in the aged dog. The distribution of β-amyloid is in the deeper cortical layers in both cases. (*C*) An 18-year-old Siamese cat exhibits a diffuse cloud of β-amyloid immunostaining in the cortex adjacent to the white matter. (*D*) In a cognitively impaired 12-year-old Beagle dog, β-amyloid immunostaining in the prefrontal cortex is extensive and affects layers II to VI. The molecular layer is free of Aβ deposition (indicated by the vertical line). (*E*) β-Amyloid immunostaining in the frontal cortex of an 86 year-old man with Alzheimer's disease shows a similar extent of β-amyloid deposition as that seen in the dog. The diffuse plaques are similar in size between the dog and the man, but dogs do not develop compact plaques (*arrow* in *E*). (*F*) A higher magnification photograph of the impaired dog in D, which illustrates the presence of intact cells (*arrows*) within the plaques. Bars in A through E = 200 μm. Bar in F = 50 μm. (*From* Head E, Milgram NW, Cotman CW. Neurobiological models of aging in the dog and other vertebrate species. In: Hof PR, Mobbs CV, editors. Functional neurobiology of aging. San Diego: Academic Press; 2001, p. 457–68; with permission.)

case with increasing age, the excess of free radicals can react with DNA, lipids, and proteins, leading to cell damage, dysfunction, mutation, neoplasia, and cell death. The brain is particularly susceptible to the toxic effects of free radicals because of its large metabolic needs, and evidence of increased brain oxidative damage has been reported in dogs [36].

Vascular insufficiency and cognitive decline

There may be a link between vascular insufficiency, decreased perfusion (eg, decreased cardiac output, anemia, arteriosclerosis, blood viscosity changes, vasospasm), and the signs of brain aging. In a subset of dogs, decreased regional cerebral blood volumes have been reported, which could be related to age-dependent cognitive dysfunction [37].

Treatment

The first step is to treat any underlying medical problem. Many age-related disease processes cannot be resolved; however, it may be possible to slow the disease-related decline (eg, dietary intervention for renal failure) or to control the clinical signs (eg, pain relief for arthritis). Even when medical problems can be resolved, the behavior problem might persist because of learning and conditioning. For example, the cat that begins to avoid its litter box because of feline lower urinary tract disease (FLUTD) may develop new surface or location preferences. Behavior problems that persist after medical problems are treated require behavior counseling.

Although behavioral modification and environmental adjustments may be needed to control specific behavior problems, cognitive decline should also be treated with a combination of nutritional therapy, drugs, and environmental management. Studies have shown that continued enrichment in the form of training, play, exercise, and novel toys can help to maintain cognitive function (ie, "use it or lose it") [38]. Keeping a regular and predictable daily routine may help to reduce anxiety, maintain temporal orientation, and keep the pet active during daytime hours so that it sleeps better through the night. Making gradual changes to the pet's household or routine can also help the senior pet to adapt better. As sensory acuity, sensory processing, and cognitive function decline, adding new odor, tactile, and sound cues (if the pet is not significantly hearing impaired) might help the pet to navigate its environment better and maintain some degree of environmental familiarity and comfort.

Nutritional and dietary therapy

One strategy in the treatment of cognitive dysfunction in animals is dietary therapy. This involves supplementing the diet of senior pets with antioxidants to improve antioxidant defenses and reduce the toxic effects of free radicals. A variety of studies suggest that high intake of fruits, vegetables, and vitamins E and C decreases the risk of cognitive decline [38,39].

A new senior diet (Hill's Prescription diet Canine b/d, Hill's Pet Nutrition, Inc., Topeka, KS) that is supplemented with antioxidants, mitochondrial cofactors, and essential fatty acids is now available. The supplemented diet improved performance on a number of cognitive tasks when compared with a nonsupplemented diet in a longitudinal cognitive study. Improved performance was observed as early as to 2 to 8 weeks after the onset of therapy [11] and continued for longer than 2 years [22,23,40,41]. In a double-blind clinical trial of 142 dogs, there was a significant improvement in cognitive signs in the group on the fortified diet (Hill's Prescription diet Canine b/d) compared with the control group [42] over 60 days. Another recent study also found that performance on a landmark task was improved by the antioxidant diet in aged Beagles and that blood concentration of vitamin E was positively correlated with improved performance [43].

Environmental enrichment and previous cognitive experience

In addition to the effects of the fortified diet, the effect of enrichment (cognitive and environmental) and previous cognitive experience were also assessed in the previously mentioned longitudinal cognitive studies in dogs. In one study, the effects of diet and environmental enrichment (exercise, novel toys, and ongoing testing) were investigated. After following these dogs for longer than 2 years, the dogs in the control group (no enrichment and no supplemented diet) showed a dramatic decline in cognitive function, whereas those in the enriched diet group or the environmental enrichment group performed better than controls on discrimination and reversal learning tasks. The combined effect of the enriched diet and the enriched environment provided the greatest improvement, however [15,40]. In a second study, aged Beagles with previous cognitive experience were compared with naive dogs. Previous cognitive experience had a positive impact on performance, which was further improved with the antioxidant-fortified diet [43]. These findings suggest that novel and continuous stimulation may aid in the reduction or prevention of cognitive dysfunction.

Drug therapy

Selegiline is a selective and irreversible inhibitor of MAOB in the dog [27]. Although the mechanisms by which selegiline produces clinical improvement in dogs with cognitive dysfunction syndrome are not clearly understood, enhancement of dopamine and perhaps other catecholamines in the cortex and hippocampus is presumed to be an important factor [44]. Selegiline increases brain 2-phenylethylamine (PEA), which is a neuromodulator that enhances dopamine and catecholamine function and may itself enhance cognitive function [45]. Selegiline may also contribute to a decrease in free radical load in the brain by inhibiting MAOB and increasing free radical clearance by enhancing the activity of enzymes like SOD [46].

Because alterations in neurotransmitter function can lead to behavior changes, such as increased irritability, decreased responsiveness to stimuli, fear, agitation, and altered sleep-wake cycles (as well as depression in human beings), antidepressants and anxiolytics might also be considered for some older pets. Because the elderly are particularly susceptible to the effects of anticholinergic drugs, it is prudent to consider therapies with less anticholinergic effects and those that are less sedating. Furthermore, anticholinergic drugs can cause increased cognitive impairment in aged dogs [31]. When benzodiazepines are considered for anxiety or inducing sleep in the senior pet, oxazepam and lorazepam, which have no active intermediate metabolites, might be safest. Recent studies suggest that cholinergic augmentation with the use of acetylcholinesterase inhibitors may have beneficial effects on cognitive dysfunction in dogs [47]; however, it is cautioned that acetylcholinesterase inhibitors currently approved for use in human beings may not demonstrate an appropriate pharmacokinetic profile for use in senior pets. Modafanil and adrafanil also may provide some benefit to certain cognitive impairments, likely through a noradrenergic mechanism. In laboratory tests, adrafanil at a dose of 20 mg/kg increased exploratory behavior and improved learning but impaired memory performance [48–50]. Consequently, adrafanil may be useful for treating particular behavioral signs, such as reduced activity, but not others.

Other treatment strategies include anti-inflammatory drugs (particularly nonsteroidal anti-inflammatory drugs [NSAIDS]) and hormone replacement therapy. Estrogen may have an anti-inflammatory effect and an antioxidant effect and may increase cerebral blood flow. Estrogen-treated female dogs made significantly fewer errors in size-reversal learning tasks than estrogen-treated male dogs or placebo-treated male and female dogs. Estrogen-treated aged female dogs made more errors in spatial memory tasks than estrogen-treated male and control dogs, however [51]. Testosterone therapy might be another consideration, because in a recent study of a small group of dogs, intact aging male dogs showed less evidence of cognitive impairment than neutered dogs [52]. Other drugs not presently licensed for use in North America that may show promise include nicergoline, an α_1- and α_2-adrenergic antagonist that may increase cerebral blood flow and enhance neuronal transmission, and propentofylline, which inhibits platelet aggregation and thrombus formation.

There are no drugs licensed for the treatment of cognitive dysfunction in cats, but there are anecdotal reports of successful use of some canine medications. The possibility of improving signs, however, must be weighed against the potential risks, which are not well established in cats. Selegiline is reported to be useful in senior cats for improving clinical signs of cognitive dysfunction, such as disorientation, increased vocalization, decreased affection, and repetitive or restless activity. In addition, in a small non–placebo-controlled study of 27 cats averaging approximately 4 years of age, selegiline was reported to be effective in improving a variety of behavioral

signs ranging from productive signs (eg, aggression, insomnia, bulimia) to deficit signs (eg, anorexia, increased sleep) [53]. Except for occasional cases of gastrointestinal upset, no adverse effects have been reported to date. Nicergoline might be dosed by dissolving a 5-mg tablet in water, giving one quarter of the solution, and discarding the rest, whereas a dose of one quarter of a 50-mg tablet daily might be considered for propentofylline.

Other therapeutic strategies

Medical conditions ranging from endocrinopathies to organ failure can also have varying effects on cognition and may lead to further accumulation and decreased clearance of free radicals. Perhaps the most significant effects on health and life span might best be achieved through weight control.

Naturopathic supplements, nutraceuticals, and homeopathic remedies have been suggested for calming, reducing anxiety, or inducing sleep. These include melatonin, valerian, dog appeasing pheromone (DAP, Veterinary Product Laboratories, Phoenix, AZ), Feliway pheromone sprays, and Bach's flower remedies (Nelsonbach USA Ltd, Wilmington, MA). Phosphatidylserine is a phospholipid that constitutes a major building block of the cell membrane. Because the neurons are highly dependent on their plasma membranes, phosphatidylserine may facilitate the activities of the neuron that are dependent on the cell membrane, such as signal transduction, release of secretory vesicles, and maintenance of the internal environment. Ginkgo biloba may improve memory loss, fatigue, anxiety, and depression in the elderly, possibly because of MAO inhibition, free radical scavenging, or enhancement of blood flow. Combination natural products that contain a wide variety of ingredients, including docosahexaenoic acid, flavonoids, carotenoids, L-carnitine, lipoic acid, ginkgo biloba, phosphatidylserine, and other antioxidants (eg, vitamins E and C), are now available from veterinary and human manufacturers. Although many of the aforementioned therapies have not been formally tested in the clinic or laboratory, they may provide an alternative, and relatively safe, treatment in pets that are refractory to standard therapies.

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