

Effect of S-Adenosylmethionine Tablets on the Reduction of Age-Related Mental Decline in Dogs: A Double-Blinded, Placebo-Controlled Trial*

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CLINICAL RELEVANCE

Oral S-adenosylmethionine (SAME) tosylate supplementation (Novifit tablets, Virbac) was evaluated as a dietary aid for the management of age-related mental impairment in dogs. Thirty-six dogs older than 8 years that had displayed signs of cognitive dysfunction for at least 1 month were selected for the study. The dogs were administered 18 mg/kg SAME tosylate ($n = 17$) or identical placebo tablets ($n = 19$) for 2 months. Concurrent behavioral treatment was forbidden. A 14-item standardized questionnaire evaluated behavior and locomotion difficulties. Compared with the placebo group, SAME-treated dogs showed greater improvement in activity (41.7% versus 2.6% after 4 weeks, $P < .0003$; 57.1% versus 9.0% after 8 weeks, $P < .003$) and awareness (33.3% versus 17.9% after 4 weeks, $P < .05$; 59.5% versus 21.4% after 8 weeks, $P < .01$). The aggregate mental impairment score was reduced by more than 50% in 41.2% and 15.8% of dogs treated with SAME and placebo, respectively, at week 8. SAME tosylate tablets proved safe and effective in improving signs of age-related mental decline in dogs.

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■ INTRODUCTION

With age, dogs may suffer a decline in cognitive function (memory, learning, perception, awareness).¹ Clinical signs commonly associated with brain aging include disorientation, decreased mental alertness, decreased activity, depression or apathy, increased anxiety, irritability, changes in interaction with owners, alterations in the sleep–wake cycle, and housesoiling.^{2–4} In a recent retrospective study, mild to severe cognitive impairment was recorded in 27.5% of dogs 11 to 12 years of age and 67% of dogs 15 to 16 years of age.⁵ Nonmedical causes of these behavioral changes are thought to be related to

quired in the synthesis and inactivation of monoamine neurotransmitters such as norepinephrine, dopamine, and serotonin.^{10–12} Through transsulfuration reactions, demethylated S-adenosylmethionine (SAME) is metabolized to glutathione, the main cell antioxidant that protects tissue against free radicals.¹³ Several studies suggest that methyl group deficiency in the central nervous system may play a role in the etiology of Alzheimer's disease.^{9,13} Important and consistent reductions of SAME concentration are found in the cerebrospinal fluid and in several brain areas of patients with Alzheimer's disease.^{14,15} Oral SAME supplementation increases

Oral SAME supplementation improves mood and cognitive measures in elderly humans with dementia.

degenerative changes, chronic brain hypoxia, damage from free radicals, and alterations in neurotransmitter concentrations in the central nervous system.^{1,6}

There are similarities between canine cognitive dysfunction and human Alzheimer's disease.¹ Neuropathologic changes include accumulation of β -amyloid plaques in similar areas of the brain, and although dogs lack the neurofibrillary tangles seen in the human disease, several authors consider that older dogs may be a good model for the study of age-related neurodegenerative conditions in humans.^{7,8}

S-adenosylmethionine (SAME) is an endogenous molecule formed from methionine and ATP in every living cell and is particularly abundant in the brain and liver.⁹ SAME is the donor of methyl groups in many different reactions catalyzed by methyltransferase enzymes. Methylation plays an important role in maintaining the fluidity of cell membranes, favoring lateral movements and unmasking of receptors within the lipid bilayers, and is re-

cerebrospinal fluid concentration of SAME¹⁶ and improves mood and cognitive measures in elderly humans with dementia.^{17,18}

Since cognitive dysfunction signs in senior dogs not affected by a general medical condition presumably are related to an Alzheimer's-like pathology, therapeutic strategies for these dogs may parallel those for humans with dementia of the Alzheimer's type.³

Based on SAME's potential beneficial effects in the brain and reported use of the compound in human psychiatry and neurology, the goal of this study was to evaluate whether oral SAME supplementation could be useful in the management of declining mental functions in senior dogs.

■ MATERIALS AND METHODS

The study was conducted as a randomized, double-blinded, placebo-controlled clinical field trial at five veterinary centers in France, Belgium, and Spain. Dog owners were required to sign informed consent forms.

Animals

Thirty-six dogs older than 8 years were included in the study by veterinary investigators; the dogs' breed, sex, and living conditions varied. The inclusion criterion was the detection of at least two behavioral problems among the following categories related to old-age mental impairment: disorientation, confusion, or learning deficits; decreased alertness or activity; decreased social interactions; change in the sleep-wake cycle; loss of housetraining; and anxiety. Exclusion criteria included primary neurologic disease and any severe sensory decline, clinically impactful heart failure (stage 2 or 3) or renal failure, diabetes, clinical hypothyroidism, hypercorticism, cancer, and infectious disease. When required, veterinarians performed complementary examinations (blood analysis, medical imagery) to rule out possible underlying medical conditions. None of the study animals was receiving treatment with psychoactive drugs, pheromones, food, or dietary supplement designed to improve behavior by the time of their inclusion in the study. Patients receiving long-term NSAIDs or glycosaminoglycan dietary therapy for arthritis could be included in the study, provided their orthopedic condition was stabilized before entering the trial and their analgesic treatment remained unchanged.

Treatments

The dogs were randomly allocated to one of two treatment groups according to a preestablished randomization list. Seventeen dogs were given SAME tosylate tablets (Novifit, Virbac; available under the same brand name in the United States, Virbac Animal Health) orally once daily (mean dose: 18.5 mg/kg) for 2 months. The other 19 dogs received identical placebo tablets (inert vehicle only) according to the same treatment regimen. Owners were instructed to administer the tablet orally either

by placing it directly in the dog's mouth or in a small quantity of food. The products were provided to investigators under the same packaging identified only by code numbers, so that veterinarians and owners remained unaware of actual treatments received by the animals throughout the study (blind evaluation). No other behavioral therapy or instruction was allowed concomitantly. Administration of any other treatment was recorded in the case report forms.

Evaluation

Clinical and behavioral evaluations were performed at baseline and then again after 4 and 8 weeks of treatment. At each examination, a standardized questionnaire (Table 1) was completed by veterinarians based on information provided by the owners. The 14-item codified grid included behavior and locomotion signs typical of geriatric dogs, and each sign was scored on a severity scale from 0 to 3 (0 = none; 1 = slight; 2 = moderate; 3 = marked). Behavior and locomotion scores were combined to calculate aggregate mental and physical scores, respectively, reflecting the global severity of the problems observed. In addition, a case-specific disability questionnaire was developed with each owner: Up to four observable daily activities found to be most troublesome for the dog at baseline were reassessed at home once every 2 weeks throughout the study period. The ability of the dog to perform each of these activities was scored by the owner on a scale from 0 (no problem) to 3 (unable to perform), and the scores were combined to calculate a case-specific geriatric disability index. At the end of the study period (week 8), the subjective opinion of each owner regarding treatment outcome was recorded as very satisfied, satisfied, hardly satisfied, or not satisfied.

Any adverse event occurring during the trial, regardless of whether it was product related,

TABLE 1. Standardized Questionnaire Used to Evaluate Behavior and Locomotion Signs in Geriatric Dogs*

<i>Parameter</i>	<i>Baseline</i>	<i>Week 4</i>	<i>Week 8</i>
Behavior Parameters			
Disorientation, confusion, learning deficits			
Learning deficits: Loss of formerly acquired knowledge (e.g., no longer sits when asking for treat), does not conform to prohibited acts or places anymore (e.g., jumps on bed), does not respond when called by name	0 1 2 3	0 1 2 3	0 1 2 3
Disorientation: Spatial orientation difficulty, has trouble finding the food bowl or exiting the door, stands at wrong door to go outside, has difficulty bypassing obstacles (goes the wrong way)	0 1 2 3	0 1 2 3	0 1 2 3
Confusion: Wanders aimlessly, seems lost at home, gets stuck in corners or behind furniture, stares into space or at walls, vocalizes without identifiable cause	0 1 2 3	0 1 2 3	0 1 2 3
Decreased alertness and/or activity			
Decreased activity: Reduction of structured “goal-oriented” activity (such as scratching at door to go outside) as opposed to aimless wandering	0 1 2 3	0 1 2 3	0 1 2 3
Decreased awareness: Pays less attention to surroundings, may not notice owner’s verbal command, seems apathetic or disinterested	0 1 2 3	0 1 2 3	0 1 2 3
Decreased social interactions			
Lack of recognition of people: Does not recognize familiar people	0 1 2 3	0 1 2 3	0 1 2 3
Decreased relationship with owner: Less demanding for care, cajolery, or game playing; decreased tail wagging; seeks attention less; may become irritated when stroked	0 1 2 3	0 1 2 3	0 1 2 3
Decreased relationship with other pets: Less frequent contacts (sniffing, playing), recent appearance of aggressiveness	0 1 2 3	0 1 2 3	0 1 2 3
Altered sleep–wake cycle			
Increased duration of sleep: Global increase of the total period of sleep over 24 hr	0 1 2 3	0 1 2 3	0 1 2 3
Broken sleep patterns: Restless, awakens, wanders, or vocalizes at night	0 1 2 3	0 1 2 3	0 1 2 3
Inappropriate toileting			
Elimination disorders: Urinates or defecates indoors (while not having exhibited such behavior in the past), less demanding to go outside	0 1 2 3	0 1 2 3	0 1 2 3
Anxiety			
Manifestations of anxiety: Apprehension, panting, moaning, shivering, licking, circling	0 1 2 3	0 1 2 3	0 1 2 3
AGGREGATE MENTAL SCORE (total)			
Locomotion Parameters			
Joint disability			
Walking difficulty: Lameness; difficulty rising, jumping, climbing or descending stairs	0 1 2 3	0 1 2 3	0 1 2 3
Pain/stiffness: Difficulty in mobilizing joints, pain on joint mobilization	0 1 2 3	0 1 2 3	0 1 2 3
AGGREGATE PHYSICAL SCORE (total)			

*Veterinarian circled relevant answer according to severity of the sign as described by owner: 0 = none, 1 = slight, 2 = moderate, 3 = marked.

was to be reported with a clear description of the clinical signs and outcome.

Statistics

Animal characteristics were compared at baseline to check group comparability before treatment. The sex ratio was compared between groups using the χ^2 test. Quantitative parameters (weight, age, age at onset of age-related mental decline, and clinical indices) were compared using Student's *t*-test; the Mann–Whitney *U* test was used for nonparametric values. In each group, the Wilcoxon signed rank test was used to test for difference in clinical parameters between baseline and week 4 or 8. The Mann–Whitney *U* test was used to perform between-group comparisons at each time point. As a continuous outcome, the case-specific geriatric disability index was analyzed by analysis of variance appropriate for a repeated measures study (mixed effect model). This model included group, time, and time by treatment interaction as fixed effects and the subjects (dogs) as the random effect. Because the effect of time and treatment was globally significant in the analysis of variance, Newman–Keuls post-hoc multiple comparisons were then performed to differentiate between groups at various time points. The proportion of dogs with fair to good response to treatments and owner satisfaction regarding treatment outcome were compared between the groups using the Fisher exact test. $P < .05$ was considered statistically significant.

RESULTS

Animal Characteristics at Baseline

All 36 dogs completed the trial and were included in the statistical analysis. Twenty breeds were represented. Cocker spaniel, fox terrier, Yorkshire terrier, Belgian shepherd, bichon frise, Scottish terrier, and shih tzu dogs represented altogether 17 individuals. Six crossbred

dogs and single individuals of the following breeds were also examined: German shepherd, beagle, bearded collie, Pyrenean shepherd, cavalier King Charles spaniel, coton de Tulear, golden retriever, Irish setter, Labrador retriever, Doberman pinscher, schnauzer, dachshund, and whippet. Baseline data did not differ between groups (Table 2).

The average age at which the age-related behavior problems appeared was 10.4 years (range: 7 to 15 years). Unusual events preceding the onset of signs could rarely be identified, but moving to a new home, death of another pet, separation from the owner, and temporary vision loss were reported in a few individuals. In most cases, the geriatric signs at baseline were described as getting more frequent or worsening (16 cases) or slowly progressing (10 cases). A chronic steady condition was recorded in the remaining 10 cases. Associated behavior problems included two cases of epilepsy and one case each of separation anxiety, storm phobia, tendency to run away, and difficult relationships with other pets. Five dogs (13.8%) had a history of previous treatments (>1 month before inclusion in the study) of behavior problems with vincamine–papaverine, clomipramine, or selegiline tablets.

Loss of formerly acquired knowledge (72.2% of dogs); reduction of structured “goal-oriented” activity (75%); decreased attention to surroundings, disinterest, or apathy (77.8%); and global increase in the total period of sleep over 24 hours (83.3%) were the signs most frequently recorded at baseline on the standardized questionnaire. Intermittent manifestations of anxiety, such as apprehension, panting, moaning, or shivering (61.1% of dogs) and restlessness, wandering, or vocalizing at night (52.8%), were also reported in a majority of cases. Moderate to marked signs of walking difficulty and joint pain or stiffness related to arthritis were recorded in 27.8% of patients.

TABLE 2. Baseline (Pretreatment) Values in Study Dogs*

Factors	SAMe (n = 17)	Placebo (n = 19)
Sex		
Males (no.)	10	12
Females (no.)	7	7
Age (yr): mean ± SD (range)	11.6 ± 2.6 (8–17)	11.5 ± 1.8 (8–14)
Weight (kg): mean ± SD (range)	16.8 ± 9.4 (3.7–35)	12.4 ± 8.4 (3–34)
Age at onset of geriatric behavior problems: median (min–max)	10 (7–15)	11 (7–13.5)
Aggregate mental score [†] : median (min–max)	12 (6–26)	10 (5–22)
Aggregate physical score [‡] : median (min–max)	2 (0–5)	1 (0–6)
Associated remarkable physical problems (no. of affected dogs)		
Marked degenerative joint disease	2	3
Lens opacity or chronic superficial keratitis	3	3
Seborrhea or chronic otitis	3	1
Benign prostate hyperplasia	2	1
Marked periodontal disease	1	1
Obesity	1	1
Ongoing antiarthritic treatments (no. of dogs receiving)		
NSAIDs	1 [‡]	1 [§]
Glycosaminoglycan dietary supplements	1 [#]	2 [#]

*None of the variables differed significantly between groups ($P > .05$).

[†]The aggregate mental and physical scores were calculated from the grading of all behavior and locomotion parameters detailed in Table 1, with each parameter scored on a 4-point severity scale (0 = none; 1 = slight; 2 = moderate; 3 = marked).

[‡]Carprofen tablets daily.

[§]Meloxicam oral solution daily.

[#]Glucosamine HCl–chondroitin sulfate tablets daily.

The most problematic activities for the aging dogs as reported by owners reflected the signs described in the standardized questionnaire. Top-ranked individual problems identified by owners in the case-specific disability questionnaire related to reduction in the global activity level of the dog (“looks tired,” “inactive,” “does not run anymore,” “does not climb stairs anymore,” “does not play anymore”), in-

ability to conform to normal daytime activity while sleeping at night (“sleeps too much,” “awakens at night,” “has nightmares”), and development of anxiety (“worried,” “feels insecure,” “tries to hide,” “follows me everywhere”). Other spontaneously reported geriatric disabilities, although ranked by owners after the previous ones in the list of problems, included orientation difficulties (“hesi-

tates to find its way at home,” “gets lost in the garden,” “does not find food bowl”), reduced ability to interact with the owner (“becomes irritable,” “aggressive at times [can bite],” “less obedient to commands,” “less demanding for cajolery”), and inability to eliminate at a desired time and correct place (“unclean,” “inappropriate toileting,” “defecates or urinates indoors”). A reduction in a dog’s activity level was often associated with reduced vigilance or alertness (42.1% of former cases) and elimination problems (45.7%), while development of anxiety was more readily associated with broken sleep patterns (31.7%).

The two groups were comparable for the clinical indices at baseline (Table 2). Basal free thyroxine levels were measured in all dogs, five of which had readings slightly below normal.

Clinical Parameters over the Study Period

Mean change from baseline in clinical parameters of the standardized questionnaire are presented in Table 3. A significant reduction of the aggregate mental score was recorded in both groups at weeks 4 and 8, but the reduction was significantly greater with SAME than with the placebo. The average mental score reduction at 8 weeks was 44.1% and 24.7% in the SAME and placebo groups, respectively. Eight of the 12 behavior parameters were improved by SAME supplementation over the study period, whereas the same was true for 3 of 12 parameters in the placebo group. Compared with placebo, SAME significantly improved the activity and awareness of senior dogs. By 8 weeks, the average improvement in the level of activity (57.1%) and awareness (59.5%) was clinically meaningful. In contrast, the improvement recorded on other parameters was moderate (e.g., 26.7% for sleep disorders) and signs of disorientation and confusion were not significantly improved by either treatment.

Considering the importance of the mental score reduction at the end of treatment, a greater proportion of dogs responded favorably to SAME therapy than placebo (Figure 1). A fair (30% to 50% reduction) to good (>50% reduction) response was recorded at 8 weeks in 13 of 17 dogs (76.5%) in the SAME group and 7 of 19 dogs (36.9%) in the placebo group ($P = .0228$).

No particular profiling of the four dogs that did not respond to SAME therapy could be identified, except that they all had signs of anxiety at baseline that did not improve much over the study period and generally had a history of chronic behavior problems. Only one of these dogs had a slightly below normal free thyroxine level initially.

No significant effect of either treatment on physical (locomotion) parameters was recorded in this study (Table 3). Clinically apparent arthritis-related joint pain or stiffness at baseline was not found to be particularly improved by SAME or placebo supplementation.

A significant reduction of the case-specific geriatric disability index was recorded in both groups beginning at 4 weeks and continuing over the course of the study ($P < .003$). Although a placebo effect was seen, owners rated SAME as more effective in improving the most problematic daily activities identified in their senior dogs (significant difference between groups at weeks 6 and 8; Figure 2). By 8 weeks of treatment, the average reduction in the geriatric disability index was 49% with SAME and 23.9% with placebo. In most cases, no complete resolution of the case-specific problems was recorded at the end of treatment. However, a large reduction of the severity score from baseline (of 2 points or more on a scale ranging from 0 [no problem] to 3 [unable to perform]) in the case-specific disability questionnaire was recorded for problems related to reduced activity in 50% of dogs after SAME therapy and

TABLE 3. Change (mean ± SD) from Baseline in Parameters of the Standardized Questionnaire after 4 and 8 Weeks of Treatment*

Parameter	SAME (n = 17)				Placebo (n = 19)			
	Week 4	P value	Week 8	P value	Week 4	P value	Week 8	P value
Behavior								
Learning deficits	-0.47 ± 0.80 [†]	.028	-0.53 ± 0.94	.028	0.05 ± 0.40		-0.11 ± 0.57	
Disorientation	-0.12 ± 0.33		-0.18 ± 0.40		-0.16 ± 0.37		-0.21 ± 0.42	
Confusion	-0.12 ± 0.78		-0.18 ± 0.88		-0.11 ± 0.46		-0.21 ± 0.42	
Decreased activity	-0.71 ± 0.59 [†]	.001	-1.06 ± 1.14 [†]	.002	-0.05 ± 0.23		-0.16 ± 0.50	
Decreased awareness	-0.65 ± 0.61 [†]	.002	-1.06 ± 0.90 [†]	.001	-0.21 ± 0.54		-0.26 ± 0.65	
Lack of recognition of people	-0.06 ± 0.24		-0.06 ± 0.24		0 ± 0		0 ± 0	
Decreased relationship with owner	-0.35 ± 0.70	.049	-0.47 ± 0.80	.028	-0.32 ± 0.75	.049	-0.37 ± 0.76	.027
Decreased relationship with other pets	-0.12 ± 0.49		-0.24 ± 0.66		0 ± 0		-0.11 ± 0.32	
Increased duration of sleep	-0.29 ± 0.59	.049	-0.59 ± 1.00	.028	-0.05 ± 0.23		-0.16 ± 0.37	
Broken sleep patterns	-0.35 ± 0.61	.027	-0.47 ± 1.00	.049	-0.37 ± 0.60	.016	-0.37 ± 0.68	.028
Inappropriate toileting	-0.41 ± 0.71	.028	-0.41 ± 0.80	.049	-0.21 ± 0.54		-0.26 ± 0.65	
Manifestations of anxiety	-0.35 ± 0.49	.015	-0.59 ± 0.87	.009	-0.32 ± 0.58	.027	-0.37 ± 0.60	.016
Aggregate mental score	-4.00 ± 2.55 [†]	<.001	-5.82 ± 4.60 [†]	<.001	-1.74 ± 1.82	.001	-2.58 ± 2.41	<.001
Locomotion								
Walking difficulty	-0.35 ± 0.86		-0.29 ± 0.99		-0.11 ± 0.32		-0.11 ± 0.32	
Pain/stiffness	-0.12 ± 0.70		-0.24 ± 0.75		-0.05 ± 0.23		-0.11 ± 0.32	
Aggregate physical score	-0.47 ± 1.33		-0.53 ± 1.46		-0.16 ± 0.37		-0.21 ± 0.54	

*All parameters were graded on 4-point severity scale (0 = none, 1 = slight, 2 = moderate, 3 = marked) at baseline, week 4, and week 8. The aggregate mental score is the total of all behavior scores. The aggregate physical score is the total of all locomotion scores. Means <0 indicate reduction of severity. Only significant P values (<.05) are shown.
[†]Significantly different from placebo at the same time point (P < .05).

only 8.3% of dogs in the placebo group. A similar large improvement was reported on complaints associated with inability to maintain a normal sleep–wake cycle in 33.3% of dogs that received SAME and 11.1% of dogs treated by placebo.

Owners Satisfaction and Tolerance to Treatment

Ten of 17 (58.8%) and 4 of 19 (21.1%) owners were satisfied to very satisfied with the efficacy of SAME and placebo, respectively (Figure 3). A significant difference was detected between the groups for the overall opinion of owners regarding treatment efficacy ($P = .0388$). The main comment recorded in the SAME group was the impression that the animal seemed more active and reactive (better interaction with the owner) under treatment.

The ease of administration of the tablet when given orally was judged as good to excellent by 77.8% of owners. The coated unbreakable tablets needed to be hidden in cold meat or cheese in the remaining cases. Tolerance to the SAME supplement was recorded as good or excellent in 16 of 17 dogs (94.1%). One dog exhibited diarrhea in the first days of supplementation. This was overcome by short-term fasting and did not require treatment interruption. No adverse event was reported in the placebo group.

DISCUSSION

To our knowledge, this is the first study reporting the use of SAME for therapy of behavior problems in geriatric pet dogs.

Under the conditions of a double-blinded, randomized study, SAME tablets proved more effective than placebo in improving activity and awareness (attention to surroundings) in senior dogs, resulting in improved quality of life. A higher owner satisfaction rate at the end of the study likely reflects the development of

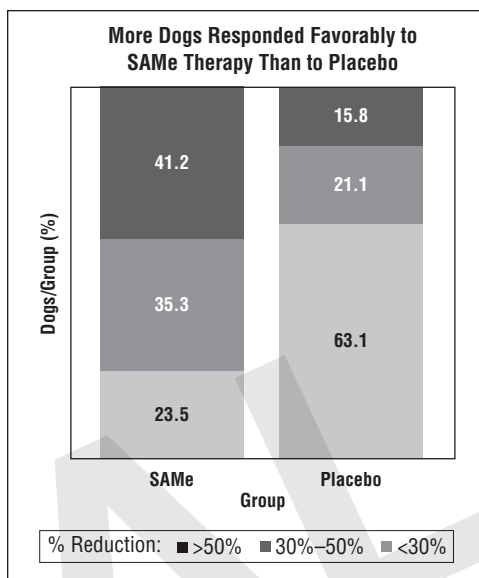


Figure 1. Percent reduction from baseline of the aggregate mental score at week 8.

better relationships between dogs and their owners as a result of the stimulatory effect of the supplementation and better performance of routine activities by senior dogs. The symptomatic therapy is supportive, providing moderate to marked improvement of geriatric behavior signs in about three-quarters of cases at 8 weeks. The effects of the nutritional supplement seem progressive over time, being significantly different from the control group between 4 (standardized behavior questionnaire) and 6 (case-specific disability questionnaire) weeks. A limitation of this study is that no posttreatment assessment was performed, precluding the evaluation of the carry-over effect of therapy beyond the 8-week administration period.

No validated scale has been published for the evaluation of canine cognitive dysfunction syndrome, perhaps because of the variety of clinical manifestations involved and assessor

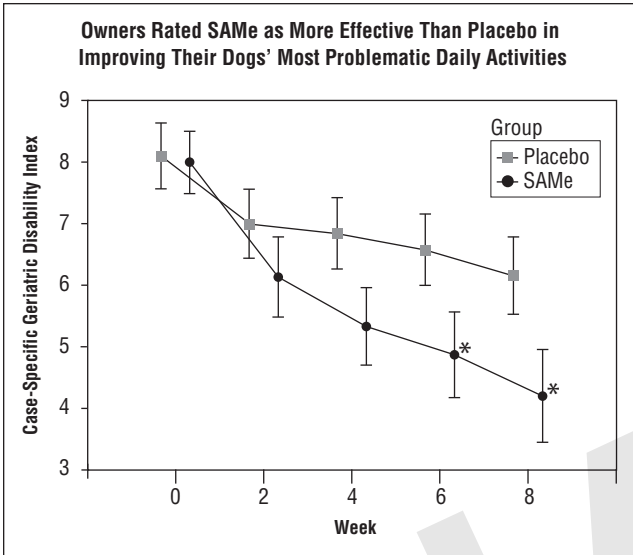


Figure 2. Mean (\pm SE) case-specific geriatric disability index over time in both groups. Owners selected up to four activities they considered most problematic for their geriatric dog at baseline and evaluated their dog's ability to perform these activities throughout the study using a 4-point scale (0 = no problem; 1 = a little; 2 = quite a bit; 3 = unable to perform). The index was calculated by adding the scores of the activities selected. *Significant difference ($P < .05$) versus placebo.

subjectivity. A number of laboratory studies have documented that elderly dogs have deficits in learning and memory compared with younger dogs as demonstrated by a decline in ability to perform a variety of cognitive tasks including discrimination, reversal, and spatial memory.^{1,19–22} Based on these laboratory findings, a number of studies have demonstrated improvement in the ability to perform these tasks using natural products including a diet supplemented with antioxidants (vitamins E and C, selenium, β -carotene, and flavonoids and carotenoids in the form of fruit and vegetable extracts), mitochondrial cofactors such as β -lipoic acid and L-carnitine, and fatty acids (Hill's Prescription Diet Canine b/d, Hill's Pet Nutrition) and a supplement containing phosphatidylserine, *Ginkgo biloba*, vitamin E, and

pyridoxine (Senilife, Innovet Italia, Saccolongo, Italy).^{22–24} Over a 2-year study, the diet provided maximal improvement when combined with a program of environmental enrichment.^{22,23}

The standardized behavior questionnaire used in the present study includes most clinical parameters classically described in cognitive dysfunction screening checklists³ and is consistent with similar scales used in previous clinical studies on psychotropic drugs against old-age behavior disorders.²² Most of the variables (8 of 12) improved during SAME treatment despite the fact that no behavioral recommendation was provided concomitantly to dog owners. The possibility that dog owners changed their behavior toward their pets because of participation in a clinical trial cannot be excluded, although the same would also be true in the

placebo group in which only 3 of 12 parameters improved over time. In addition to stimulation of activity and awareness, SAME treatment—but not the placebo—significantly decreased learning deficits, sleep duration, and elimination problems at weeks 4 and 8, albeit to a lower extent. This may explain why no significant difference was detected on the latter parameters versus the control group. It is clear, however, that SAME supplementation had little effect on disorientation and confusion disorders or lack of recognition of people.

To more closely reflect individual patient responses and measure day-to-day functional ability, a patient-specific evaluation approach was conducted with owners in this study (the case-specific disability questionnaire). This method to record and monitor activities that

appear to be restricted in individual patients was adapted from controlled studies evaluating nutraceuticals on geriatric osteoarthritic dogs,²⁵ since both physical and mental impairment can affect a dog's quality of life. While both treatments improved the disability index, reflecting owners' expectations, the magnitude of improvement was higher with SAME, showing a particular benefit to stimulate the dog's willingness to play, interact with its owner, or eliminate in desired places, as subjectively rated by owners.

These behavioral results obtained with 18.5 mg/kg SAME tosylate in senior dogs are consistent with clinical data reported in elderly human patients using similar doses. An increase in fast brainwave activity was recorded a few hours after ingestion of an acute nutraceutical dose (400 mg) of SAME by human volunteers, reflecting a vigilance-promoting mode of action.²⁶ In two double-blinded, placebo-controlled studies on elderly patients evaluated by means of electroencephalographic mapping and psychometric tests, a daily SAME intake of 400 to 1,600 mg produced changes typical of activating antidepressants of the thymoleptic type (e.g., imipramine, amitriptyline).^{27,28} In a further study examining the effects of 800 mg SAME daily on perceptual and cognitive brain function by means of electroencephalographic mapping and low-resolution electromagnetic tomography, similar antidepressant-like pharmacologic changes were recorded, and subacute treatment over 1 week produced changes consistent with a nootropic-like action (nootropic drugs are substances that preferentially improve intellectual and memory performance in patients with cognitive disorders).²⁹ Several meta-analyses of clinical trials on a large number of patients demonstrate that SAME is more active than placebo, and as effective as classical tricyclic antidepressants, in the treatment of depression in humans.^{10–12,30,31} In clinical studies, elderly depressed patients

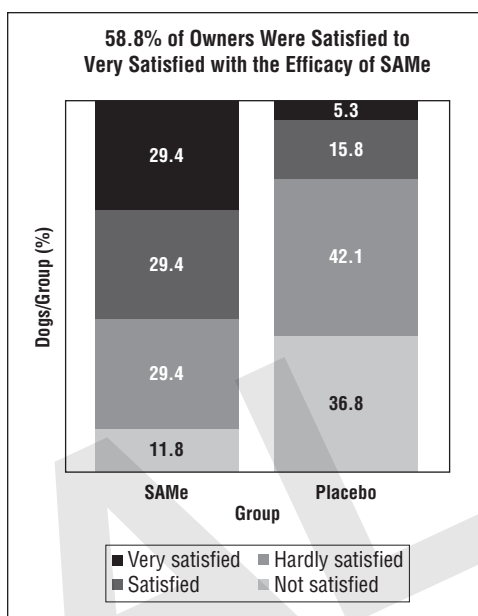


Figure 3. Owner satisfaction with treatment outcome at week 8.

showed greater SAME-induced changes than younger ones, supporting the idea that SAME has a more pronounced effect in deficit states.^{28,31} In patients with Alzheimer's dementia, 3 months of oral SAME (1,200 mg daily) produced a sharp increase in SAME and monoamine metabolites in the cerebrospinal fluid and improved mood, cognitive measures, and speed of mental processing.^{13,14,16–18}

The mechanism of action of SAME in the brain is still putative. The clinical effect of SAME may result from its role as a methyl donor to biogenic amines, which influence neurotransmitter metabolism, and from its role in the methylation of cell membrane phospholipids, which increase membrane fluidity and receptor function.¹⁴ There is evidence that SAME is involved in the synthesis and turnover of monoamines.¹³ The administration of SAME is associated with an increase in noradrenaline, serotonin, and dopamine in selected brain

areas in laboratory rodents.³²⁻³⁵ SAME may also affect neurotransmitter receptor systems.¹³ Treatment with SAME increases β -adrenergic binding in old rat cerebral membranes^{36,37} and restores a normal density of muscarinic³⁸ and prolactin³⁹ receptors in the brain of aged rats and rabbits. This effect is thought to be mediated by increased neuronal membrane fluidity, as a result of the conversion of phosphatidylethanolamine, a phospholipid present in cell membranes, to phosphatidylcholine through SAME-dependent methylations.¹⁰ Increased membrane fluidity facilitates the movement of receptor proteins within the lipid bilayer and neurotransmission by producing more efficient receptor–neurotransmitter coupling.¹² It is not known to what extent these mechanisms are relevant in the canine species. However, cognitive dysfunction in old dogs is associated with a similar set of factors that may be influenced by SAME, particularly neurotransmitter abnormalities in the central nervous system.³

It is noteworthy that 8 weeks of dietary supplementation with SAME in this study did not significantly improve the physical signs of osteoarthritis (walking difficulty, joint pain or stiffness) when present in aged dogs. This contrasts with human clinical field trials on degenerative joint disease in which long-term daily administration of SAME (400 to 1,200 mg/day) was shown to be effective in reducing similar symptoms (morning stiffness, pain on movement).^{40,41} In double-blinded comparative trials, SAME was even found to be as effective as NSAIDs (e.g., ibuprofen, celecoxib) to control signs of human osteoarthritis in the long term (several months), albeit its onset of action was slower.^{42,43} This is attributed to a chondroprotective effect, as orally administered SAME was found to enter the synovial fluid^{9,44} and increase proteoglycan synthesis in experimental animal models.^{45,46} Demethylated SAME undergoes a “transsulfuration” pathway that pro-

duces a number of sulfur compounds (notably glutathione) and transsulfate glycoaminoglycans.⁴⁴ The lack of significant beneficial effect of SAME on locomotion parameters in this study may be related to a too-short observation period or the relative low number of dogs with moderate to marked osteoarthritic signs at baseline (27.8%), which was not an inclusion criterion. Alternatively, SAME simply may not be effective enough to relieve arthritic pain in dogs. In any case, it points out that the stimulation of activity and awareness noted in the senior dogs in the present study cannot be attributed to an improvement in musculoskeletal condition.

A significant placebo effect was reported in this study on three behavior parameters, resulting in a significant decrease of the aggregate mental score in the placebo group (–24.7%). Owner rating of dogs’ capability to perform routine daily activities at home was also improved. This reflects the subjective nature of the behavioral attributes measured and owners’ sensitization about the potential benefits of the test product for their dogs in a blind evaluation. It can also result from the owners paying more attention to their dogs during the study. The placebo effect in clinical trials of drugs or dietary therapy to manage behavior conditions underlines the need for controlled studies in this area.

At a dose of 18.5 mg/kg, SAME tosylate was well tolerated in the geriatric dogs, traditionally a more susceptible subset of the canine population. Self-resolving gastrointestinal upset may rarely occur with SAME intake, as reported in a single individual in this study. This is in line with the low incidence of side effects reported in human clinical trials with the compound, in which mild gastrointestinal complaints (such as heartburn and nausea) are sometimes reported.^{9,12} It would be interesting to further evaluate the effect of treatment on

blood biochemistry and hematologic parameters in dogs, which was not investigated in this study.

CONCLUSION

SAME tosylate tablets administered daily for 2 months proved to be a safe and effective oral supplement for improving signs of mental decline in dogs older than 8 years. Further long-term studies on a larger number of geriatric dogs are required to refine appropriate treatment regimens and explore interaction with other drugs.

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