



S-adenosylmethionine

(SAME) and cognitive dysfunction in dogs

A roundtable discussion

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Disease Background: Cognitive dysfunction syndrome

Dr. Gary Landsberg: For our discussion today, we have gathered veterinary behaviorists and practitioners from North America and Europe, a psychiatrist who treats people with depression and Alzheimer's disease, and a pharmacologist with a special interest in drugs that affect the nervous system.

Let's begin by defining age-related cognitive dysfunction in dogs. In North America, we use the term *cognitive dysfunction syndrome* to describe a spectrum of clinical signs that relate to perception of stimuli and to memory and learning. The clinical signs, which can start months or years before owners become aware of them, are primarily caused by age-related changes in the brain.

It is important that practitioners identify the clinical signs. Several studies have looked at the frequency of cognitive dysfunction in dogs. In one, researchers found that at least 68% of dogs 15 to 16 years old had one or more clinical sign of cognitive dysfunction.¹ Twenty-eight percent of dogs aged 11 or 12 years also had at least one sign.

The diagnosis of cognitive dysfunction is a diagnosis of exclusion. Practitioners must remember two things. First, in aging pets, medical problems can contribute to many of the same clinical signs of cognitive dysfunction so you have to rule out medical causes. Second, even if you find medical causes, the dog can still have concurrent cognitive dysfunction.

Clinical Signs

Landsberg: Now let's talk about the clinical signs associated with cognitive dysfunction. In North America, we often use the acronym DISHA, which stands for disorientation, interaction changes with family members and other pets, sleep-wake cycle alterations, housetraining loss, and activity level changes (both

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increase in repetitive activities or decreased overall activity). What are the most common signs associated with early cognitive dysfunction?

Dr. Amanda Florsheim: Dogs are usually presented to me because of housesoiling or a disturbance in their sleep-wake cycle. These signs disrupt owners' lives, so they are what general practitioners see.

Landsberg: Owners don't always report these subtle signs. Do you have any suggestions for identifying these signs as early as possible?

Florsheim: At my clinic, we are implementing a standard questionnaire for dogs older than eight years. This form asks questions about these subtle signs, such as: Have you seen a decrease in play? Does your dog seem to sleep more during the day? We ask about subtle signs early, rather than waiting for the more dramatic signs to appear later.

Dr. Valerie Dramard: As the disease progresses, disorientation becomes another sign of cognitive dysfunction. The dog gets lost in the garden or in its neighborhood. Or when you open the

Florsheim: We run a complete blood count, serum chemistry profile, urinalysis, and urine culture to rule out as many medical causes as we can. We also conduct a thorough neurologic exam.

Landsberg: You should do a complete workup that is not more extensive than necessary. In some cases, an MRI or CT scan might be appropriate, whereas in cases with no neurologic abnormalities or with signs related to other organ systems, these tests might be unnecessary.

Several years ago, I was on a panel of the American Animal Hospital Association that set up senior care guidelines. Those guidelines recommend annual examinations at middle age and twice-a-year examinations as pets reach their senior years. This is the time to take a good behavioral history. It is critical to talk with the owners at every year's checkup—these are the pet's caregivers.

Pets and people

Landsberg: Dogs have been used as models for aging in people for about 15 years. Dogs do not get Alzheimer's disease per se; but they do undergo brain changes similar to the early changes in Alzheimer's disease. Using

Dr. Teodoro Bottiglieri: In human medicine, the term dementia comprises many different types of cognitive dysfunction. The most common form is Alzheimer's type dementia, which makes up 70% of all cases. The pathologic hallmark of this form of dementia is the deposition of beta-amyloid protein in the brain, which leads to the formation of senile plaques. Studies in dogs have shown that beta-amyloid protein and plaques are present in the brain and as in humans the amount of beta-amyloid burden is correlated with the degree of cognitive decline. The second most common form of dementia in humans is vascular dementia occurring in about 17% of all cases. In aged dogs cerebral vascular changes can also be present.

Landsberg: Dogs do not progress to the full Alzheimer's changes and don't develop such irreversible or major changes like people do. That's why they are used as models for early Alzheimer's changes and why therapeutics might be more effective in animals.

Numerous vascular changes have been identified as well. A couple of the therapeutics available in Europe for dogs are directed at treating blood flow changes in the brain.

Dr. David Mischoulon: It is striking how similar the presenting clinical signs are for cognitive dysfunction in dogs and people. In people, we see a lot of the same problems with sleep abnormalities, changes in activity, and disorientation. We also note a couple of differences. First, soiling is usually not a problem in Alzheimer's patients until very late in the disease. Second, people have a tremendous capacity for denial, which a dog doesn't have. The dog cannot deliberately try to hide its deficits, compensate for them, or argue with you when you tell them something is wrong. Sometimes it is hard to convince families that this is a dementia and requires treatment. Are dog owners prone to denial when they start seeing problems in their pets?

Florsheim: Many are and some don't bring up problems with their veterinarian because they think the pet is just getting older.

door to let it outside, the dog is on the wrong side, standing next to the hinges. That is quite bizarre to owners.

Diagnosis

Landsberg: If a dog is brought in for housesoiling or night waking, how would you determine it has cognitive dysfunction, as opposed to some other problem?

neuropsychological tests, researchers have found memory and learning deficits beginning as young as 6 years of age.

Researchers have also examined the brains of older animals and have found increasing ventricular size, neuronal loss, and an increasing beta-amyloid deposition.² How does that correlate with your knowledge of changes in the brains of people with Alzheimer's?





Landsberg: If we can get owners to understand the disease process, the signs to look for, and the fact that therapies exist, they might volunteer the information much earlier.

Mischoulon: With people, the fact that we now have treatments for Alzheimer's disease that can alter the course of the illness is a strong incentive for people to open up. People are more likely to admit a problem exists if they know something can be done.

Treatment options

Landsberg: In North America, we have a couple of agents used in animals with cognitive dysfunction. Dr. Florsheim, would you please review these treatment options.

Florsheim: The drug that most general practitioners in North America turn to for dogs with cognitive dysfunction is selegiline (Anipryl—Pfizer). Most practitioners report that about half of owners are satisfied with the results. I think practitioners feel fairly limited in what they have to offer clients.

Landsberg: Selegiline is classified as a monoamine oxidase-B (MAO-B) inhibitor, but we don't know its true mode of action in dogs. It enhances catecholamine transmission and perhaps serves as an antioxidant because superoxide dismutase has been shown to increase with selegiline therapy. In clinical trials³ about 80% of animals showed improvement in some clinical signs within one to two months of therapy. Is selegiline used in people?

Mischoulon: In people, selegiline is used primarily as an antidepressant and for treatment of Parkinson's disease. Most MAO inhibitors on the market are MAO-A inhibitors, which can cause side effects and complications if taken with certain foods. People are reluctant to follow a strict diet when taking MAO-A inhibitors, so these antidepressants have mostly fallen by the wayside. However, the MAO-B inhibitors like selegiline don't have those same issues, particularly at lower doses. So, selegiline has made a comeback in the form of a patch. Selegiline has improved cognition in

Alzheimer's disease, based on a few clinical trials, but it is not FDA-approved for dementia at this time.

Landsberg: Because selegiline is fairly selective for MAO-B, it doesn't have any food restrictions with it. But what drugs should be avoided?

Florsheim: Don't use selegiline with selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressant drugs. You need a two-week washout period if you transition a dog from one drug to another. Depending on the dog's clinical signs, that transition time can be difficult for an owner.

Landsberg: Amitraz, a parasiticide, is an MAO inhibitor and tramadol may have some effect on serotonin, so these are more drugs to use with caution. In general, selegiline is fairly devoid of side effects. It either helps the animal or it doesn't.

Some natural compounds also exist for the treatment of cognitive dysfunction in North America. Hill's Prescription Diet b/d Canine is the only diet tested in both laboratory and clinical trials. The diet is a sodium and

enrichment and this fortified diet is the most effective in improving learning and memory.⁴

Florsheim: I've had relatively good success with b/d. However, so many older dogs have other dietary restrictions. For example, you can run into problems when you have a dog with cognitive dysfunction and food allergies. You have to pick the health problem on which you are going to focus your attention.

Landsberg: Some supplements on the North American market for cats and dogs have similar ingredients to what is added to b/d. However, very few of these have been tested or there have been few clinical trials.

Behavioral Therapy

Landsberg: When a dog is diagnosed with cognitive dysfunction, what specific things can owners do to help the pet? What behavior modification techniques, enrichment programs, and drugs can a veterinarian offer?

Florsheim: Behavior modification and management are important in cases



phosphorus restricted senior diet with added alpha-lipoic acid and L-carnitine, which help mitochondria function more efficiently. It is also supplemented with antioxidants, such as vitamin E, vitamin C, selenium, flavonoids, carotenoids, and omega-3 fatty acids. This diet was tested in a laboratory for more than two years. From that study, the researchers learned that a combination of brain

involving any older dog, whether it is showing obvious signs of cognitive dysfunction or not. Most owners place a lot of importance on puppy training. As dogs get older, emphasis on training declines and there is less focus on providing environmental stimuli and social structure. These older pets are supposed to know the house rules. But the need for training and structure don't

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go away with older animals. In addition, research suggests that training and enrichment can slow the progress of cognitive dysfunction in dogs. For dogs already suffering some of the effects, providing simple, clear, direct cues so they know what is expected and giving short enrichment exercises may work. Keeping them focused and providing easy-to-follow instructions are important for these pets.

Landsberg: Also, pain management might be critical in keeping an older pet's life enriched; if it's not in pain, an older pet can move around more. Feeding and manipulation toys are good options for older dogs. Taking walks instead of runs, and playing tug games instead of chase games are all alternative forms of enrichment for senior dogs.

Florsheim: You must provide these pets with clear cues and instructions and a stricter social structure. Owners may need to take the dog out more frequently or may need to start placing the pet in its crate again, if it was originally crate trained. Feeding toys are good, but for dogs with cognitive dysfunction, keep them simple; they may

candles or aromatherapy products such as lavender to help the pet find its way around. Owners can make many adjustments to keep dogs enriched and functional. Use rewards, not punishment. And be very consistent.

Dramard: I tell owners not to shout at their dogs. Old dogs can become quite depressed. The owner must be quiet, calm, and empathetic to avoid stressing the dog. When the dog doesn't sleep well, the owner should increase its activity during the day. The dog will be more tired at night and might sleep better. Let the dog sleep in the owner's bedroom; old dogs can become anxious, so perhaps sleeping close to the owner would help it sleep better.

Drug therapy

Bottiglieri: Do you use acetylcholinesterase inhibitors in dogs? I know these have limited success in people.

Landsberg: At CanCog, a private company in Toronto, Ontario, Joseph Araujo is doing his PhD thesis on muscarinic decline in the brain of senior dogs and has researched the effects of scopolamine on cognition in older dogs.⁵ He found that when old

improving learning and memory tests in dogs. Most of these drugs, however, have side effects or are cost-prohibitive and are not currently licensed or available for use in dogs.

Mischoulon: In people, cholinesterase inhibitors are a temporary treatment measure. They gently alter the course of the illness and slow its progress. There is no evidence that they stop or reverse the illness. The earlier you institute the treatment, the better the outcome.

Landsberg: What other drugs or psychotropic agents do you recommend to help with restlessness and sleep-wake cycles?

Dramard: Some veterinarians use a drug like acepromazine or diazepam, but I do not feel that it is advisable to give sedatives to older pets because you can depress them more and worsen any cognitive dysfunction. A drug such as clomipramine or fluoxetine could be used. It should take effect after a few days. I think it is better to use a psychotropic or antidepressant drug if you see signs of anxiety or depression.

Landsberg: So for chronic anxiety, ongoing agitation, or ongoing depression in an elderly pet, you might need these drugs. However, as we mentioned, you have to be careful with anticholinergic drugs and be sure to discontinue selegiline before using clomipramine or fluoxetine. For short-term use, are there other drugs that are shorter acting and don't take a few days or weeks to take effect?

Florsheim: You could use a benzodiazepine, such as alprazolam.

Landsberg: So it is okay to use a short-acting drug just before specific events such as bedtime, thunder anxiety, or departure anxiety. Dr. Mischoulon, you treat depression, mood disorders, and anxiety in older people. Where do psychotropic drugs fit in when treating your senior patients?

Mischoulon: Psychotropic drugs are a mainstay of treatment. Depression



"The earlier you institute the treatment, the better the outcome."

- Dr. David Mischoulon

not be able to use the more complex ones. When taking older dogs outside, be sure they aren't overstimulated. Rather than taking them to a park with 50 other dogs, stay in the front yard and give them short periods of exercise.

Landsberg: If a pet can't walk well, put ramps in. If the pet can't see or hear well, use odor cues such as scented

dogs are given anticholinergic agents, their ability to perform learning and memory tasks declines very rapidly. Young dogs are not affected in the same way. If a cholinergic decline is a component of cognitive dysfunction in older dogs, giving anticholinergic compounds can cause learning and memory problems for them. Early studies on cholinesterase-inhibiting compounds showed some promise in



and mood disturbances are common with dementia and we often treat both in the elderly. About two dozen FDA-approved antidepressants and as many sedatives are on the market. A lot of new ones have come out in the past few years that help people sleep but are less habit-forming. We can alleviate depression and anxiety in elderly patients much better than we could before. On the other hand, there is always concern about side effects because the elderly are much more vulnerable to them. We always have to start with a low dose and increase it gradually.

Landsberg: Veterinarians may use fluoxetine to try to re-establish more normal sleep cycles and a benzodiazepine as a sleep agent in older pets. Are there similarities in how you use these in people?

Mischoulon: It is very similar to what we would do.

A new therapeutic tool: SAME

Landsberg: We now have a new therapeutic tool available for cognitive dysfunction in dogs—S-adenosylmethionine, commonly known as SAME. Dr. Bottiglieri, please tell us about the molecule itself.

Bottiglieri: S-adenosylmethionine (SAME) is produced naturally in the body and every cell has the ability to synthesize it. In fact de-novo synthesis of SAME is required because dietary sources do not provide sufficient amounts. It is one of the most versatile molecules involved in a myriad of biochemical reactions, second only to adenosine triphosphate (ATP) as a pivotal molecule in biochemistry and cellular function. It is formed when methionine and ATP combine.

The function of SAME is to donate a methyl group to small molecules such as the neurotransmitters dopamine and epinephrine and to macromolecules, such as DNA, proteins, and lipids. The effects of methylation are as varied as the molecules that are methylated, so it is difficult to know the exact mechanism

of action of SAME in the treatment of depression or dementia since many pathways could be involved.

Landsberg: Many products used to slow or treat cognitive dysfunction in older pets have antioxidant mechanisms. Does SAME play an antioxidant role?

Bottiglieri: Yes. SAME is a precursor molecule to the transsulfuration pathway that leads to the synthesis of glutathione. Preclinical and clinical studies have shown that after administration of SAME there is an increase in glutathione in the blood and liver. Other studies have shown that SAME can modulate glutathione levels and markers for lipid peroxidation in brain tissue.⁶⁻⁸

Landsberg: With aging, is there a change in endogenous SAME production?

Bottiglieri: There is experimental evidence to show that tissue levels of SAME are significantly decreased in 30-month old rats compared to younger rats. The decline in SAME concentration was evident in most organs, including the brain. Studies in people have also shown that there is an age-related effect in the concentration of SAME in cerebrospinal fluid (CSF). In the first year of life SAME concentrations are relatively high and begin to decline thereafter. Interestingly this decline with age follows the concentration of folate levels in CSF. There have not been any studies, which have looked at SAME concentrations in blood or CSF from elderly subjects. However, folate levels tend to decline and homocysteine levels tend to increase with advancing age.⁹⁻¹²

Landsberg: In veterinary medicine, we have used SAME for years in cases of liver disease. We are less familiar with its use as a supplement for the brain. Dr. Mischoulon, tell us about using SAME and its use for cognition in elderly people.

Mischoulon: In people, SAME has been studied primarily as an antidepressant. There are at least 45 published clinical

Table 1. Most common clinical signs of cognitive dysfunction at baseline

Increased total amount of sleep during a 24-hour period	83.3%
Decreased attention to surroundings, disinterest, apathy	77.8%
Decreased purposeful activity	75.0%
Loss of formerly acquired knowledge (including elimination behaviors)	72.2%
Intermittent anxiety (apprehension, panting, moaning, shivering)	61.1%

trials examining different forms of SAME. It is generally accepted in the psychiatric field that SAME is effective for depression. Currently, it is one of the more popular over-the-counter agents that people use if they want to self-medicate for depression.

One of the appealing qualities of SAME, as opposed to some other natural products, is that it doesn't appear to have any adverse interactions with other medications. My group has focused on using SAME as an adjunctive agent. We have found that by giving SAME in addition to another antidepressant, we get a more robust antidepressant response in the patient. We have published a study demonstrating this, and have other such studies in progress. SAME helps with the whole spectrum of depressive symptoms, including difficulties with cognition, memory, and concentration, as well as mood enhancement. SAME has few adverse effects and is well tolerated. It is not hepatotoxic and is, in fact, beneficial to the liver. In many ways, it is the ideal medication for an elderly person.

Not much clinical data on SAME's effect on dementia exist. We know that SAME deficiencies are associated with increases in compounds that are toxic to the brain. We know that SAME administration in animals can reverse or attenuate some of the adverse effects.

Landsberg: In clinical practice, we do see some senior pets that appear to be depressed, but in veterinary medicine, we don't use the term depression except when talking about

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Table 2. Study results: Improvement in total mental score and geriatric disability index as measured on Day 60

	Novifit	Placebo
Total mental score	44.1%	24.7%
Geriatric disability index	49.0%	23.9%

the apathetic state. However, more commonly we see signs of agitation, sleep-wake cycle changes, and lack of responsiveness to their owners. Could S-AdoMet be able to target these areas?

Mischoulon: Absolutely. All of those signs are common in major depression and in dementia. Because people with depression can have their symptoms alleviated by S-AdoMet, I would expect similar benefits in animals with those signs.

Landsberg: Is there any clinical or laboratory test that might indicate depression or when S-AdoMet might be of benefit for people or animals?

Mischoulon: One of the holy grails of psychiatry has been to develop an objective test for depression. But

depression exhibit abnormalities.

Although right now we don't have a good test for depression or for predicting whether S-AdoMet will be effective, the current investigations are promising. In a few years, I think we will start seeing practical data that we can use to manage our patients.

Application of S-AdoMet (Novifit®) in clinical practice

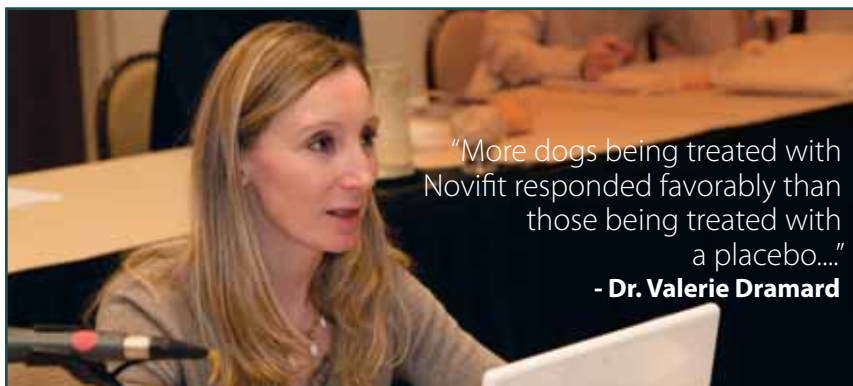
Landsberg: Novifit is licensed as a S-AdoMet product in Europe. Dr. Dramard, please describe your recent clinical study of Novifit.

Dramard: One clinical trial was conducted in 2005 in France, Belgium, and Spain to evaluate whether Novifit could be used to manage declining cognitive function in senior dogs. Thirty-six dogs over 8 years of age were chosen for the study. All dogs displayed two or more of the following behavioral signs: disorientation, confusion, learning deficits, decreased alertness, decreased activity, decreased social interaction, changes in sleep-wake cycle, housesoiling, and anxiety for at least one month. Exclusion criteria were incapacitating disease, clinical infections, and the use of psychotropic

Clinical and behavioral examinations were performed on Days 0, 30, and 60. A standardized behavior questionnaire with 12 items was completed by the attending veterinarian on the basis of information given by the owners. The most common clinical signs reported are listed in *Table 1*, page 5.

Each clinical sign was scored using a scale of 0 to 3 according to the intensity and all scores were added to calculate a total mental score. In addition, a case-specific disability questionnaire was developed with each dog owner, who identified up to four unique observable problems. These clinical signs were assessed by the dog owners and also scored 0 to 3 points according to the gravity of the problem on Day 0 and each following week during the two-month study period. The sum of these scores was called the geriatric disability index. The average age at which age-related problems appeared was 10.4 years. Ten dogs had a stable chronic condition that included one or more of the following behaviors; separation anxiety, storm phobia, tendency to run away, difficulty interacting with other pets, or epilepsy. Five dogs had a history of previous treatment for cognitive dysfunction with vincamine, papaverine, clomipramine, or selegiline. Five different dogs had low levels of free T₄ on Day 0 that was not treated because of lack of attributable clinical signs.

More dogs being treated with Novifit responded favorably than those being treated with a placebo tablet, as measured by improvement in total mental score and geriatric disability index (*Table 2*). For the dogs treated with Novifit, 11 out of 17 dogs (64.7%) showed a fair or good response to treatment (*Table 1*, page 7). Only seven out of 19 dogs (36.8%) treated with the placebo showed a fair or good response to treatment. After two months of Novifit supplementation, the average improvement in the level of activity was 57.1%. The average improvement in the level of awareness was 59.5%. The improvement in number of learned behaviors, most notably elimination behavior was



for now the gold standard is still the clinical interview. Throughout the years, different biochemical approaches have been tried, such as the dexamethasone suppression test or measurement of the metabolites of serotonin, dopamine, and norepinephrine. All of these tests lack sensitivity and specificity. A lot of people with depression have normal profiles, and a lot of people without

drugs, pheromones, or nutraceutical specific diets to improve behavior in the previous months.

Study dogs were administered one weight-appropriate Novifit tablet per day directly by mouth or with a small quantity of food. The minimum S-AdoMet dose administered was 18 mg/kg/day. Any other modality to address behavioral problems was forbidden.



clinically meaningful at 57.1%.

By contrast, the average improvement recorded for signs such as confusion (33.3%) or increased total amount of sleep over 24 hours (26.7%) was moderate.

More than half of the owners of dogs assigned to the Novifit treatment group (58%) were overall satisfied or very satisfied with the product as opposed to 21.1% of owners of dogs who received the placebo tablet. They found Novifit easy to give to their dogs (77.8%) and thought that their dogs tolerated Novifit well (94.1%). We saw during this trial that the effect was progressive over time. Improvement was seen at one month and again at two months. We don't know what would happen during a longer treatment period because the trial was conducted for two months only.¹³

Landsberg: What is the minimal amount of time you would expect to see effectiveness of SAME and the longest time you would wait to see effectiveness?

Dramard: It depends on the case. My protocol is that I begin with SAME and propose a recheck in two weeks. If they notice at least a little improvement, we continue. If there is no progress, I add another drug. I wouldn't start with this protocol if the dog appears to have underlying disease that needs to be addressed.

Bottiglieri: SAME has a good safety profile. Diarrhea has been reported in people, though it's transient and resolves itself. Other complaints in people have been headaches and some nausea.

Mischoulon: We are currently running two SAME studies in people, and stomach upset and diarrhea are the most common side effects. The side effects in dogs seem very similar to what we see with people.

Landsberg: If you are seeing gastrointestinal side effects with SAME, would you suggest continuing treatment, stopping use of the drug, or lowering the dose of the drug?

Dramard: I suggest stopping the drug, waiting for two or three days, and starting again at a lower dose than the first time.

Mischoulon: Typically, antidepressants require six to eight weeks to work. So a good clinical trial should run for at least eight weeks. There are some studies in which people who were taking SAME,

particularly in combination with another antidepressant, improved fairly quickly, usually within two weeks. This parallels Dr. Dramard's findings that animals improve within a couple of weeks.

Landsberg: Does administering SAME early on in the disease process—rather than later—make it more effective at resolving or controlling clinical signs?

Bottiglieri: Management of dementia is dependent on early detection and intervention. We know that the damage caused by the deposition of beta-amyloid in the brain is irreversible. I think early pharmacotherapy gives you the best chance for success. It would be interesting to know the effect of SAME when given as a prophylactic treatment for dementia in dogs. That would let us see the effect of SAME treatment before clinical signs of dementia appear.

Landsberg: Studies to date have been about improving the clinical signs instead of catching the disease early and slowing the progress. Is there enough evidence to say that if older animals were just developing early signs of cognitive decline, SAME could slow progression of the disease?

Bottiglieri: From a biochemical standpoint it makes sense. It would be interesting to perform a double-blind,

placebo-controlled trial to compare the efficacy of SAME when given before clinical signs of dementia have appeared. My prediction is that the group on SAME would benefit the most.

Mischoulon: One area I would like to see explored is the role of neurotropic agents in the prevention of disease, particularly in high-risk individuals. For example, in a family with many cases of Alzheimer's, a family member might benefit from starting an agent like SAME or ginkgo biloba earlier, even before symptoms exist. We all agree that the earlier we treat Alzheimer's, the better the outcome.

Landsberg: Are there any contraindications for SAME?

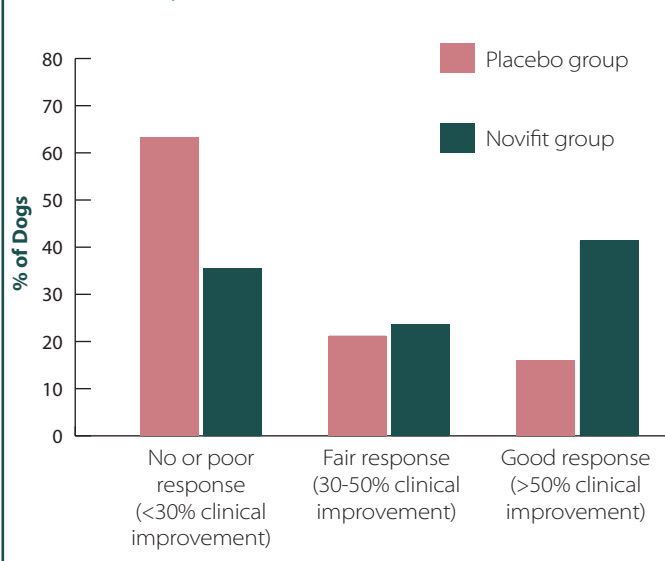
Dramard: There are no label contraindications.

Landsberg: Are there any contraindications in human medicine?

Mischoulon: Some people with bipolar disorder who are depressed and treat themselves with SAME may cycle into mania. I don't know if there is an analogous disorder in dogs, but I would watch for agitation in an animal that has just started receiving SAME.

Landsberg: You hear about the range in quality of nutraceuticals. Is there a

Figure 1. Study results: Overall response to treatment as measured on Day 60



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difference in the quality of brands of S-AdoMet, as there is in some of the other herbal products?

Mischoulon: I am asked that a lot. A lot of the early oral forms of S-AdoMet were quite unstable and lost their efficacy quickly. That affected a lot of the early S-AdoMet trials. The new tosylated forms on the market are much more stable and have a long half-life. As far as S-AdoMet goes, I would be confident in the brands that come from reputable organizations. I tell patients to shop around but go to health food and drug stores that are reputable. Be careful about shopping on the Internet and buying an unknown brand, especially one that makes outlandish claims. A lot of them may be very poor quality preparations. It's the same principle when buying medicine for pets.

Landsberg: Nutraceutical products are not as regulated as pharmaceuticals, so make sure that the product is from a reputable manufacturer. Does the packaging matter? Is there a problem with loose pills in a bottle versus individual blister wrap packaging?

loose tablets. Is that correct?

Bottiglieri: Yes. That is how some of the early S-AdoMet tablets were sold, and it was a problem. In the year 2000, we tested some S-AdoMet tablets in the lab and found out that some of them contained 0% S-AdoMet.

Landsberg: Knowing what you have learned today, as a practitioner, how would you use Novifit in treating your cognitive patients, once it becomes available in the United States.

Florsheim: I would consider recommending it for older patients in general. Because of its neuroprotective effect, I would discuss its use with clients during every senior exam while we're discussing the changes that are going to occur in the pet. It could be a good supplement for dogs that are showing signs of early cognitive decline and dogs showing no signs yet. I also think it is a first line of intervention for patients showing the more extreme signs.

Landsberg: Trying a supplement that has virtually no side effects and then considering other drugs as either an



Bottiglieri: To ensure long-term stability, the S-AdoMet tablets should be stored in a sealed foil strip. If the tablet is exposed to moisture it will degrade and oxidize within months.

Landsberg: In other words, you would avoid bottles that are packaged as

alternative or adjunct therapy later would be the safest and most logical route to take.

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