

Supplementation Effects of an Alpha-Casozepine and White Fish Muscle Hydrolyzed Complementary Feed on Canine Separation-Related Disorders and Quality of Life of Dogs and Their Pet Caregivers

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Abstract

Background: Separation-related disorders are prevalent in dogs and can result in problem behaviours such as inappropriate elimination, destructive behaviour, and distress vocalizations which occur when a caregiver is absent or perceived as absent. Numerous natural products are marketed for managing these behavioural issues in dogs; however, few, if any, of these products have documented evidence of their positive effects in veterinary behaviour. **Purpose:** This open, multicentric clinical trial aimed to assess the effect of a new supplement containing alpha-casozepine and fish muscle hydrolysate on the separation-related problem in dogs and the impact on the quality of life of dogs and their caregivers. **Material and Methods:** Fifty-one dogs with clinical signs compatible with separation-related problems were included. The dogs were supplemented with a complementary feed (Zylkene Plus, Vetoquinol, France) for 30 days. Separation-related behaviour assessment (SRP), emotional disorders assessment (EDED) and the quality of life (QoL) of the pets and their pet caregivers were assessed at baseline and at the end of the study by the veterinarians. In addition, caregivers were asked to rate their dog's SRP weekly after enrolment using the same questionnaire that the veterinarian used at the beginning of the study. **Results:** There was a statistically significant improvement in the SRP, EDED, and QoL scores ($P < 0.0001$). The mean glob-

al SRP score decreased by 32% between baseline and D7, 41% between D0 and D14, 47% between D0 and D21, and 49% between D0 and D30. The percentage of dogs in a normal state (EDED < 12) increased during the study from 26% in D0 to 62% at D30, and the percentage of dogs with scores related to anxieties decreased from 40% at D0 to 17% at D30. On day 30, there were significant improvements in QOL scores compared to the baseline. **Conclusion:** The results of this study support the hypothesis that the combination of alpha-casozepine and fish muscle hydrolysate is a promising and effective option to reduce the frequency and severity of separation-related behaviour in dogs and improve the quality of dogs and their caregivers.

Keywords

Alpha-Casozepine, Fish Muscle Hydrolysate, Canine Separation-Related Disorders, Dogs

1. Introduction

Separation-related behaviour problems have been estimated at 20% of the dog population [1].

In contrast, dogs with separation-related behaviour problems engage in undesirable behaviours when left alone. The most common are destruction and excessive vocalization, including whining and barking. Less common problem behaviours include inappropriate elimination (urination and defecation), self-injurious behaviour (e.g. over-grooming), increased or repetitive motor activity (e.g. pacing), attempts to escape, trembling, salivation, and depression [2].

Dogs that engage in excessive vocalization when left alone are likely to prompt complaints by neighbours and visits from local authorities. Sherman [3] notes that living with a dog with separation-related problems causes emotional and financial distress at home, affecting the quality of life (QoL), which can lead to the dog's surrender. Indeed, separation-related problem behaviours are commonly cited reasons for relinquishing dogs to animal shelters.

The management of separation-related problems consists of environmental control, behaviour modification, and medications. However, environmental control and behaviour modification require commitment and regularity in the household routine and often a deliberate weakening of the caregiver-pet bond. In addition, behaviour modifications can sometimes be challenging for the caregiver who has difficulty reducing contact with the dog or in homes with multiple occupants where it is difficult to enforce changes in routine [4].

When dogs do not respond to behavioural therapy, pharmacological agents can be prescribed to manage dog behavioural symptoms, such as fluoxetine, benzodiazepine, selegiline amitryptiline, and clomipramine [5]. In addition, due to their cerebral suppressant properties, such treatments can have sedative effects [5] [6].

Across veterinary disciplines, there is interest in the use of alternative treatment modalities, including acupuncture [7] [8], homoeopathy [8] [9] [10] and nutraceuticals [11] for the treatment of common medical and behavioural disorders [11] [12] [13] [14]. Caregivers often perceive these options are safer with fewer side effects.

Numerous natural products are marketed for managing behavioral issues in dogs; however, few, if any, of these products have documented evidence of efficacy in veterinary behaviour.

The present study evaluated a new supplement containing alpha-casozepine and fish muscle hydrolysate (Zylkene Plus, Vetoquinol, France) for the management of separation-related problems in dogs. This multicentric clinical trial aimed to assess the effect on signs associated with separation-related problems in dogs and the impact on the quality of life of dogs and their caregivers.

2. Materials and Methods

2.1. Design

This study was designed as an open-label, multicenter, prospective trial.

A total of 11 veterinary clinics, including general and behaviourist practices, participated.

2.2. Study Population

The dogs were eligible for the study if they met the inclusion and exclusion criteria.

Inclusion criteria: Occurrence for at least one month of one or more of the following manifestations of separation-related problems: inappropriate urinating and defecating, barking and howling, chewing, digging and destruction, pacing, exaggerated greetings, rearranging the caregiver's things.

Exclusion criteria were dogs with severe chronic disease or receiving supplement products, pheromones, or any other psychotropic medication for the behaviour condition in the previous 10 days.

All dogs had to be in good health to be included in the study, based on history and complete physical examination. Dogs were included in the study regardless of breed, sex, origin (conditions of adoption) or lifestyle.

Caregivers were eligible for the study if they were able to provide a stable home environment for the duration of the study (no major changes in household routine, vacation longer than 3 days without the dog, extended guest stays, or change in family members at home (including new pets)). Caregivers also had to commit to complying with the supplement administration.

2.3. Supplementation and Administration

The caregiver administered the supplementation orally daily for 30 ± 2 days, 30 minutes to 1 hour before separation. The capsule could be opened, and the powder mixed with food or given as a treat according to **Table 1**.

Table 1. Dosage of Zylkene Plus.

Animal weight	Zylkene Plus 75 mg	Zylkene Plus 225 mg	Zylkene Plus 450 mg
[2 - 10] kg	2 capsules	-	-
[10 - 15] kg	-	1 capsule	-
[15 - 30] kg	-	-	1 capsule
[30 - 60] kg	-	-	2 capsules

Specific behavioural therapy instructions were not given to keep a reproducible environment among the subjects.

3. Outcome Measures

The dogs were examined as described in the following summary of the protocol (**Figure 1**).

At baseline and $D30 \pm 2$, veterinarians performed a clinical examination, an evaluation of dog behaviour related to separation (SRP) (**Table 2**), an evaluation of the dog's emotional disorders (EDED) (**Table 3**) and an evaluation of the quality of life (QoL) of dogs and their pet caregivers (**Table 4**).

Weekly after enrolment, caregivers were asked to rate their dog's SRP using the same questionnaire the veterinarian used at the beginning of the study (**Table 2**). In addition, the caregivers were asked to rate their dog's behaviour (destructive behaviour, rearranging, excessive vocalization, inappropriate urination, inappropriate defecation, escaping, shadowing, excessive greeting, excessive salivation and pacing) on a 4-point continuous scale from 0 = never to 3 = always, resulting in global SRP ranging from 0 to 42.

The emotional disorders evaluation (EDED) (**Appendix 1**) in dogs allows the practitioner to assay basic behaviors of the dog (*i.e.* eating, drinking, grooming, play, aggression, exploratory behavior) as well organic signs. The scale produces a numeric result of 9 to 45 points, with normal dogs scoring between 9 and 12. Dogs with anxiety-related disorders score between 18 and 30 [15].

4. Statistics

Statistical analysis was performed using validated Stata Statistical Software: Release 16; College Station, TX: StataCorp LP.

For continuous variables, the following descriptive statistics were performed: mean, standard deviation, sample size, minimum, and maximum. For qualitative or binary variables, absolute and relative frequencies were presented.

Scores at $D30 \pm 2$ were compared with the initial score (D0) using the Wilcoxon matched-pairs signed ranks test. Statistical significance was stated if $P < 0.05$.

5. Results

5.1. Participants

A total of 51 dogs were recruited for the study. Among them, 4 dogs were not

included in the analysis (supplement discontinuation, incomplete questionnaire, wrong posology). The dogs ranged in age from 6 months to 13.4 years of age and in weight from 2.5 to 49 kg. Demographic data are shown in **Table 4**.

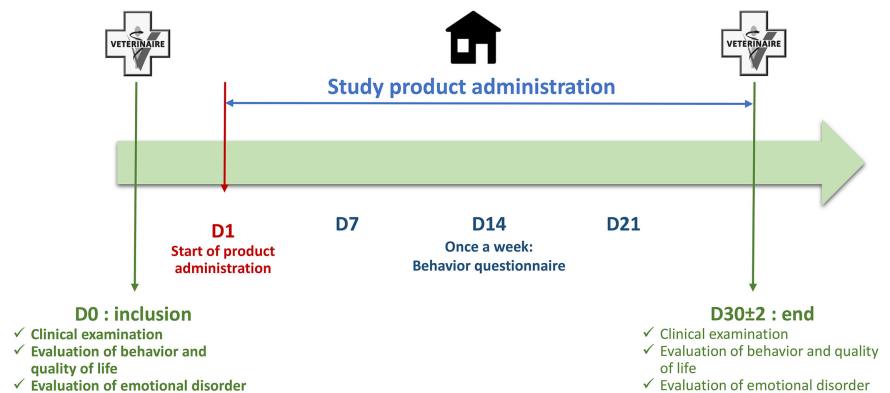


Figure 1. Summary and timeline of the study.

Table 2. Separation-related problem questionnaire. Each question is rated on a 4-point continuous scale from 0 = never to 3 = always, resulting in a global SRP ranging from 0 to 42.

Separation-related behaviour questionnaires

Does your dog insist on following you around when you're home?

Does your dog become anxious at the sound of car keys or when you put on your coat or shoes to go out?

Does your dog bark or whine excessively within 30 minutes of your departure?

After you leave, does your dog act depressed?

After you leave, does your dog have a loss of appetite or ignore treats left out for him?

Does your dog destroy property only when you are away (chewing, breaking, tearing, scratching, biting at windows, doors and exits, etc.)?

Does your dog urinate at home only when you are away?

Does your dog defecate at your home only when you are away?

Does your dog attempt to escape from his kennel/pen/room when you are away?

Does your dog show rearranging behaviour (*i.e.* moving household objects around without destruction)?

Does your dog have excessive salivation in your absence?

Does your dog is pacing (constantly walks in a circle or back and forth) in your absence?

Does your dog regularly have diarrhoea, vomit, or lick excessively in your absence?

Does your dog exhibit an excessive greeting on your return (jumping, hyperactivity, barking, more than 2 - 3 minutes)?

Table 3. Quality of life questionnaire. Each question was scored on a 4-point continuous scale from 0 = not at all to 3 = very much.**Quality of life questionnaire**

How severe and disturbing is your dog's anxiety?

How much are your dog's playing or working activities disturbed by his anxiety?

Does your dog's anxiety have an impact on its relationship with you, other family members or other dogs?

How much has your dog's disease changed its usual habits (change in place where he is allowed to sleep, live, eat, way it which it is walked, etc.)?

How much time do you lose for your dog's anxiety (administration of therapies, home cleaning, veterinary consultations, etc.)?

How much effect has your dog's anxiety on your tiredness?

How much are your usual activities and/or those of your family disturbed by your dog's anxiety (leisure, vacation, walks, work, etc.)?

How much impact does your dog's anxiety have on your expenditure (cost of treatment, veterinarian, etc.)?

How much effect does your dog's anxiety have on causing emotional distress (feeling of guilt, powerlessness, sorrow, regret, anxiety, nuisance, disgust, anger, frustration, etc.)?

How much physical uneasiness/discomfort is your experience due to your dog's anxiety (offending odour, feeling of dirtiness at home, aesthetic nuisance, etc.)?

Does your dog's anxiety have a negative impact on the relationship between family members (between spouses, between parents and sons, with relatives and friends, etc.)?

Table 4. Demographic data of included dogs.

Parameter	Statistics	Total
Number	N	47
Breed	N	Boxer (2), Shih Tzu (2), Yorkshire Terrier (3), Beagle (1), Beauceron (1), Bichon Frise (1), Bolognese (1), Cane Corso (1), Cavalier King Charles Spaniel (1), Chihuahua (1), Cocker Spaniel (3), Coton du Tulear (1), Dachshund (1), German Shepherd (1), English Bulldog (1), French Bulldog (3), German Pinscher (1), Golden Retriever (1), Griffon (1), Jack Russell Terrier (2), Miniature American Shepherd (1), Miniature Pinscher (1), Parson Russell Terrier (1), Poodle (1), Rottweiler (1), Small Munsterlander (1), Springer Spaniel (1), White Swiss Shepherd (1), Whippet (1), Wire Fox Terrier (1), mixed breed (9)
Sex	N	21 females including 15 neutered 26 males including 14 neutered
Other pets in house	N	none (21) 1 pet (15) 2 pets (9) 3 pets (1) 4 pets (1)
Lifestyle	N	indoor and outdoor (38) mostly indoor (9)
BW (kg)	mean ± sd [min. - max.]	15.1 ± 10.9 2.5 - 49.0
Age (years)	mean ± sd [min. - max.]	4.5 ± 3. 0.6 - 13.4

5.2. Outcome Measures

5.2.1. Separation-Related Problem Behaviour Assessment

To evaluate the improvement, the overall score for each behaviour was evaluated. From Day 7 to the study end, there was a statistically significant improvement in the severity of behavioral symptoms. The mean global SRP score decreased by 32% between D0 and D7, 41% between D0 and D14, 47% between D0 and D21, and 49% between D0 and D30, with a mean total score of 16.7 ± 6.0 at D0 and 8.6 ± 5.9 at the end of follow-up (Figure 2).

5.2.2. Emotional Disorder Evaluation

At the end of the study, there was a statistically significant improvement on the EDED scale, as shown in Figure 3. Thirty-four cases (72%) had a lower EDED value at D30 compared to D0, 8 (17%) presented the same value at both visits, and 5 cases (11%) presented a higher EDED value at D30 compared to D0. In addition, the percentage of dogs in a normal state (EDED < 12) increased during the study from 26% at D0 to 62% at D30. The percentage of dogs with scores related to anxieties thus decreased from 40% at D0 to 17% at D30.

5.2.3. Quality of Life

The mean QoL score before and after supplementation was 13.34 ± 6.4 and 9.5 ± 6.7 . There was a significant improvement in total QoL scores after the supplement intervention compared to Day 0 ($P < 0.0001$), as shown in Figure 4. The QoL was improved by at least 30% for 74% of the dogs.

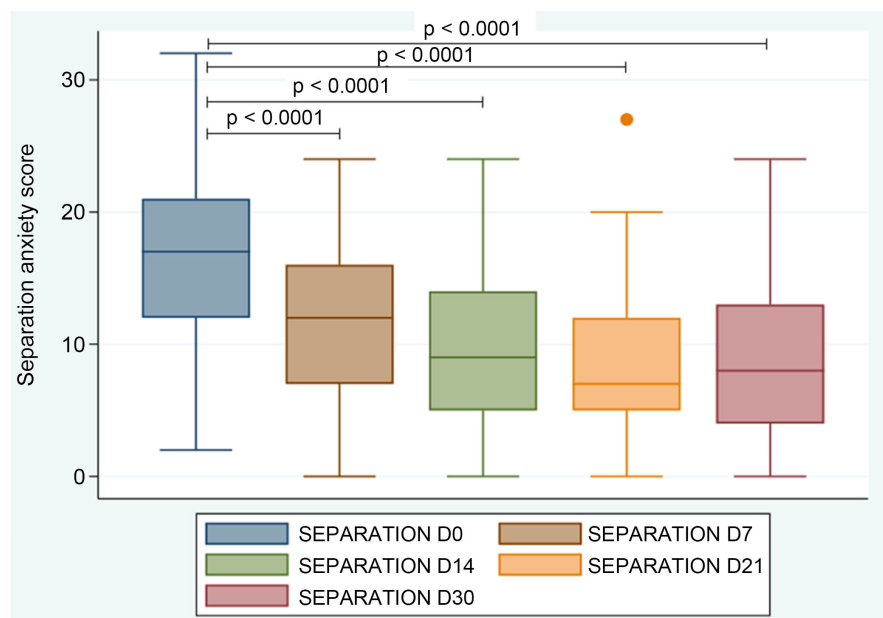


Figure 2. Distribution of the total separation-related problem score per visit through box and whisker plots. Comparison between baseline and final assessments revealed that the percentage improvement of excessive barking, destructiveness, inappropriate urination, escaping, and pacing was 48%, 62%, 72% and 60%, respectively. Dots represent values above the 90th percentile.

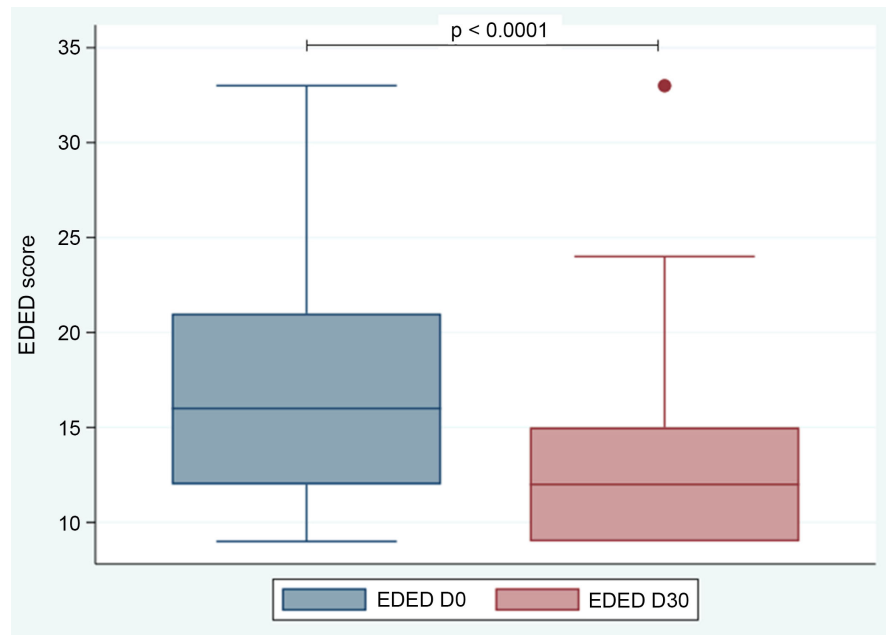


Figure 3. Distribution of the total EDED score per visit through box and whisker plots. Dots represent values above the 90th percentile.

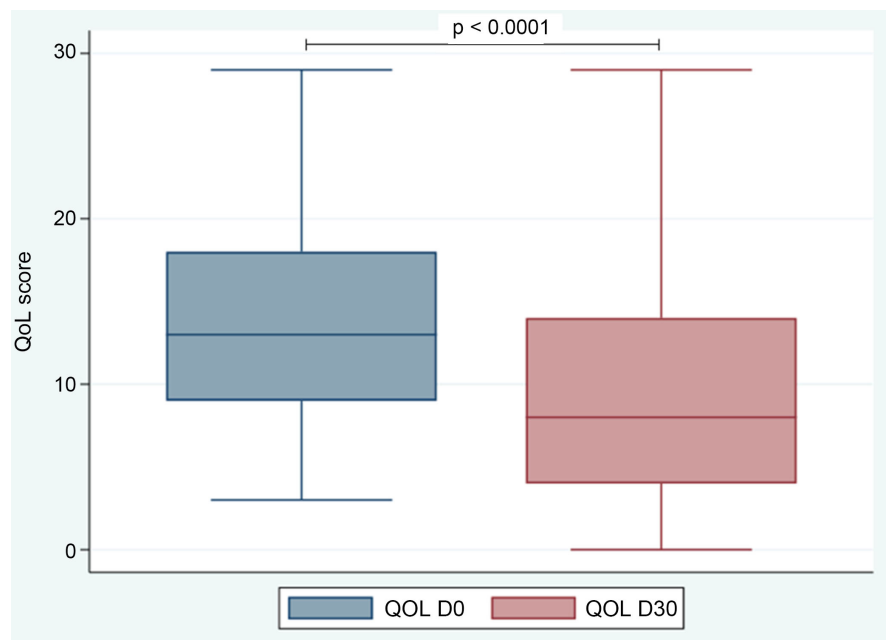


Figure 4. Distribution of the total QoL score per visit using box and whisker plots.

When comparing before and after supplement, all questions showed a decrease in scores except questions 8 and 11 (How much impact does your dog's anxiety have on your expenditure? Does your dog's anxiety negatively impact the relationship between family members?).

6. Discussion

This open, non-controlled study aimed to evaluate the effect of a complementary

feed containing alpha-casozepine and fish muscle hydrolysate in reducing the frequency and severity of separation-related behaviour signs in dogs and the impact on their quality of life. The effect was evaluated based on three different assessments: 1) separation-related problem behaviour assessment (SRP); 2) emotional disorders scale (EDED); and 3) the quality of life of pets and their pet caregivers (QoL).

The results of this study support the hypothesis that the combination of alpha-casozepine and whitefish muscle hydrolysate can be an effective method for managing separation-related behavioural signs in dogs. Furthermore, the results show that it can also improve the quality of life of dogs, their caregivers, and their emotional state.

Analysis of the SRP assessment revealed a significant decrease in the overall score for each behaviour at different times. A statistically significant improvement in the frequency and severity of behavioral symptoms has been observed as soon as D7. The mean global SRP score decreased by 49% at D30 compared to the baseline. Comparing the baseline and final assessments, the percentage improvement for excessive barking, destructiveness, inappropriate urination, escaping and pacing were 48%, 62%, 72% and 60%, respectively.

Quality of life (QoL) is a term used to evaluate general well-being, and it is defined as “the degree to which an individual enjoys his life”. In medicine, QoL is often assessed in terms of how disease negatively affects it [16]. As in previous studies, the evaluation of QoL can be interesting when studying options for disease management [17] [18]. Although patient care remains the first goal, considering the caregiver feelings can be relevant, as managing many behaviours in pets is time-consuming. When prescribing therapy, the veterinarian must not only take into account the effectiveness of the drugs prescribed but also the compliance [19].

Thus, effective treatment of anxiety disorders is not only a necessity for the health and welfare of the pet but also to improve the problem for the caregiver and ultimately restore the bond between caregiver and pet.

This present study confirmed the hypothesis that supplementation with a complementary feed containing alpha-casozepine and fish muscle hydrolysates significantly improved the QoL of dogs and their caregivers. Furthermore, one month after the beginning of supplementation, there was a significant improvement in total QoL scores compared to baseline.

At the end of the study, there was a statistically significant improvement in the EDED scale. The percentage of dogs in a normal state (EDED < 12) increased during the study from 26% at D0 to 62% at D30. The percentage of dogs with scores related to anxiety thus decreased from 40% at D0 to 17% at D30.

Environmental and behavioural modification and pharmacological therapy are often indicated to deal with the problem and address the pet’s well-being [20]. For example, behavioural advice for separation-related problem behaviours can include reducing the dependency of the dog on the caregiver, removing punishment for separation-related behaviours, providing activities for the dog to engage in when left alone, and systematic desensitization [20]. However, pet caregivers

received no behavioural advice in this study to avoid confounding factors in interpreting the results.

The study has some limitations that need to be considered. First, the study was an open, non-controlled study, meaning there was no control group to compare the results with and increase the validity of the results. The lack of a placebo control means that caution is required in interpreting these results, but it does not invalidate them. Second, the sample size was relatively small, which could affect the generalizability of the results. Additionally, the study did not include video recordings of the dog's behaviour after the caregiver left. Video recordings can provide valuable insights into the dog's behaviour when left alone and help monitor and assess the frequency and severity of separation-related problems.

7. Conclusion

Despite the limitations mentioned above, the study's findings suggest that Zylkene Plus may be a promising supplementation option for dogs with separation-related problems. The decrease in the frequency and severity of symptoms indicates that the product may effectively manage this behavioural problem. Furthermore, the potential improvement in dog and pet caregivers' quality of life is an essential consideration when evaluating the efficacy of any complementary feed.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Appendix 1

Behavior type	Specific behavior	Score
Centripetal		
Feeding	Normal appetite	1
	Hyperphagia (with regurgitation and reingestion) ¹	3
	Anorexia/hyporexia	4
	Dysorexia	5
Drinking	Normal drinking	1
	Carries empty water bowl around (ritual) ²	2
	Chews at water without swallowing ³	3
	High-frequency drinking (documented)	5
Self-stimulatory	Normal cleaning behavior	1
	Excessive licking, nibbling ⁴	4
	Stereotyped nibbling, dizziness, turning on itself (or other stereotypies) ⁵	5
Sleep	Normal (or no change)	1
	Increase in sleep, hypersomnia ⁶	2
	Insomnia, during sleep (and hyposomnia) ⁷	3
	Wakes up shortly after falling asleep, anxiety at time of going to sleep (and restlessness) ⁸	5
Centrifugal		
Exploratory (scanning)	Normal	1
	Inhibited	2
	Frequent avoidance responses	3
	Increased, hypervigilant	4
	Oral	5
Aggression (defense)	No aggression or aggression stable (no increase or decrease)	1
	Irritation-related aggression	3
	Fear-related aggression	4
	Displays both fear and irritation aggression	5
Learned social behavior	Unchanged	1
	No submission response	2
	No self-control when playing	2
	Bites without growling	4
	Steals, does not drop stolen objects	5
Specific learned-behavior	Same response capacity (allowing for disease or age)	1
	Arbitrary responses	3
	No response to previously learned behaviors	5

Continued

	Normal	1
	Periods of tachycardia and/or tachypnea	2
	Diarrhea, colic	2
Physical exam ⁹	Dyspepsia (and ptyalism)	2
	Increased emotional micturition	3
	Acral lick granuloma (and extensive lick alopecia)	4
	Obesity	4
	High-quantity drinking and urination (PU/PD)	4

Total

EDED scale: Centripetal, internal factors; centrifugal, external stimuli; PU, polyuria; PD, polydipsia.

¹Hyperphagia with regurgitation and reingestion. The dog eats rapidly, display spasms, followed by vomiting. It then reingests what it has just expelled and resumes its meal. This behaviour appears regularly (1 meal in 2).

²Carries empty water bowl around. The dog moves or carries its bowl toward one or several family members. This behaviour stops as soon as the bowl is filled.

³Chews at water without swallowing it (dipsomania). The dog nibbles the water and spreads it around its bowl while swallowing very little.

⁴Excessive licking, nibbling. A dog that is licking or nibbling itself, then spontaneously stops.

⁵Stereotypic nibbling, dizziness. When there is licking or nibbling that does not stop spontaneously (the caregivers must stop the dog or divert its attention) or else dizziness or any other stereotypy (e.g. licking of the face, jumping, wandering).

⁶Increase in sleep, hypersomnia. When the duration of sleep is longer than the age norm (+25%).

⁷Insomnia, during sleep. Awakenings appear more than 90 minutes after going to sleep.

⁸Wakes up shortly after going to sleep, anxiety at time of going to sleep. The dog awakes in the 30 - 45 minutes following going to sleep. Prior to going to sleep the dog may display moans, excitement, and a search for contacts, as if it is afraid of going to sleep.

⁹In order to take the physical examination into account, all the manifestations observed must be scored and counted.