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Effects of alpha-casozepine (Zylkene) versus selegiline hydrochloride (Selgian, Anipryl) on anxiety disorders in dogs

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Zylkene;
selegiline;
Anipryl;
Selgian;
EDED scale

Abstract After a first study showing efficacy on anxiety disorders in cats, the putative effects of alpha-casozepine (a tryptic bovine αs1-casein hydrolysate) on anxious disorders in dogs was investigated. The trial was conducted against a control molecule, selegiline. Thirty-eight dogs were recruited within veterinary practices by certified behaviorist surgeons. This 56 day trial, against the reference molecule, selegiline, showed that both products were efficient to decrease the EDED score and no statistical difference was found between their success score. Owners assessment was also statistically perfectly equivalent. Due to this efficacy, and to its safety, alpha-casozepine (Zylkene) should be considered an option by the veterinary surgeon for the biological management of anxiety beside the compulsory behavior modifications.

Introduction

Anxiety disorders in dogs are an important issue in veterinary behavioral medicine. Although various definitions for these disorders have been proposed, depending primarily on whether the authors believe that there exists such a thing as "normal anxiety" (Overall, 1997; Dodman and Shuster, 1998) or not (Pageat, 1995, 1998; Mege et al., 2003), it is generally agreed that anxiety-related conditions are one of the main groups of behavioral disorders occurring in dogs.

The many possible causes of anxiety states range from internal causes such as hormonal imbalance (Clarke et al., 1998) and genetic vulnerability (Tancer et al., 1990; Uhde et al., 1992) to external causes such as species-inappropriate

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living conditions, ambiguous social relationships and inappropriate/unfair punishment.

The management of anxieties, fears and phobias may require inducing behavioral changes and possibly stress reduction training programs to improve dogs' abilities to cope with stressful situations. In addition to behavioral therapy, drugs have been developed to promote and speed the rate of animals' recovery. Drugs used currently as anxiolytics are numerous and belong to different classes (Loo et al., 1990) including:

- anxiolytics:
  - beta-blockers
  - alpha-2 agonists
  - morpholines
  - benzodiazepines (the use of which varies considerably from one country to another); and
- antidepressants
  - tricyclic antidepressants (TCAs)
  - selective serotonin reuptake inhibitors (SSRIs)
  - monoamine oxidase inhibitors (MAOIs).

However, the use of other compounds that have not been included in the classical drug classification scheme is now increasing. Two of these are:

- pheromones
  - dog appeasing pheromone is used to deal with many anxious conditions, mainly during development (Mills et al., 2003; Pageat and Gaultier, 2003; Vienet-Legué, 2006); and
- neutriceuticals
  - alpha-casozepine has been studied in classical laboratory rat models of anxiety (based on the use of conditioned defensive burying and elevated-plus maze paradigms, for instance) (Schroeder et al., 2003; Violle et al., 2006) and under various stress-inducing conditions in the case of human beings (Lanoir et al., 2002; Messaoudi et al., 2002, 2005). This compound has proved to be an effective means of relieving anxiety in cats with social phobias (Beata et al., 2007).

Alpha-casozepine originated in the alpha S1 casein portion of milk. It is similar in spatial structure to gamma amino butyric acid (GABA) (Miclo et al., 2001), and is a decapeptide obtained from α-S1 casein by tryptic hydrolysis. It has an affinity for benzodiazepine receptors, particularly a sub-category of GABA-A receptors, as reviewed previously (Beata et al., 2007).

Many owners are reluctant to give their dogs psychotropic drugs and express concerns to veterinarians that they are worried about 'addiction.' Although few of the pharmaceuticals discussed have any addiction potential, and none is addictive at therapeutic levels, owners often feel reassured when veterinarians are able to offer 'natural' compounds. These compounds also must be shown to be efficacious. Efficacy data based on clinical trials provide practitioners with the evidence they require to prescribe such compounds with confidence.

We provided evidence recently of the efficacy of alpha-casozepine in cats in a study where the effects of the drug were compared with those of a placebo, so it seemed worthwhile to carry out similar trials with dogs. An initial study using a placebo showed promising effects in relieving anxiety in dogs (Beata et al., unpublished). For ethical reasons, we decided to conduct this study by comparing alpha-casozepine with a known, 'control' compound, selegiline, which is marketed in veterinary medicine for the treatment of anxiety disorders (in Europe) (Pageat, 1995, 1998, 2005; Mege et al., 2003) and old-age cognitive changes (in the United States) (Ruehl et al., 1998; Kitani et al., 2002; Landsberg, 2005). All work was done in compliance with the Good Clinical Practices guidelines (European Directive 92/18/CEE and European Directive III/3767/92).

Dog trials

Justification of the trials

Anxiety in dogs is an important issue. Although the definition of anxiety varies among studies, all authors agree that anxiety does exist in dogs. Pageat (1995, 1998) has defined anxiety as an emotional state characterized by an increase in the probability of fear-like emotional reactions being triggered in response to any change in the internal or external environment. This emotional state leads to a loss of self-control and adaptability. Based on our own records of more than 2,700 cases, anxious states account for up to 70% of all behavioral disorders occurring in dogs.

Anxiety in dogs is not only a psychological issue. The first signs of an anxious state often include visceral reactions. Many human and veterinary studies have been published about the relationships between dermatologic signs and anxiety (Hashiro and Okumura, 1997; Mege, 1997; Virga, 2003), gastro-intestinal signs and anxiety (Longstreth and Wolde-Tsadik, 1993; Levenstein, 1999; Marion, 2002), neurologic signs such as seizures and anxiety, and cardio-respiratory signs and anxiety (Pedersen et al., 1995; Yang et al., 1997; Toren et al., 1999; Tamam et al., 2000; Couture, 2001). Given this pattern, all veterinarians should be interested in relieving anxious states because they are often faced with the consequences of these states in their daily practice.

The management of anxiety is a challenge for veterinarians. To be as effective and efficient as possible an integrated treatment should include behavior modification targeting the roots of the anxiety-provoking situation, whenever possible, and the use of biologic agents (psychotropic drugs, pheromones, and nutraceuticals). Many veterinarians do not use biologic agents as a routine part of their treatment. This is regrettable because if we go back to our definition of anxiety, anxiety leads to a loss of adaptability. The use of biologic compounds may be the best way to quickly decrease the manifestation of the signs

Table 1 EDED scale used to include dogs in the study

EDED Scale*				D0	D14	D28	D42	D56
Centripetal		Bulimia, insatiable appetite, hyperphagia	3					
		Hyporexia, anorexia	4					
	Food	Dysorexia (alt.hyporexia, bulimia)	5					
		Normal	1					
		Bulimia with regurgitation and reingestion	3					
		Normal	1					
	Drink	High-frequency (documented polydipsy)	5					
		Chewing water without swallowing	3					
		Carries empty bowl around	2					
		Normal grooming behaviour	1					
	Grooming	Licking, biting itself	4					
		Stereotyped licking, tail-chasing	5					
		Normal	1					
	Sleep	Increased, hypersomnia	2					
		Insomnia , hyposomnia	3					
		Sudden waking-up, anxiety when time to sleep	5					
		Normal	1					
		Simply inhibited	2					
	Exploratory	Increased arousal, hypervigilance	4					
Centrifugal		Oral	5					
		Frequent avoidance responses	3					
		Unchanged	1					
	Aggressions	Irritation-related aggression	3					
		Fear-related aggression	4					
		Irritation- and fear-related aggressions	5					
		Steal, does not give back stolen objects	5					
	Social learned behaviors	Bites without growling	4					
		No submission response	2					
		No self control when playing	2					
		Normal/unchanged	1					
	Specific learned behaviors	Same responses	1					
		Arbitrary responses	3					
		Nearly no more responses	5					
		Normal	1					
		Tachycardia-tachypnea	2					
	Physical examination	Diarrhea	2					
		Vomiting, dyspepsia	2					
		Emotional micturition	3					
		Acral lick granuloma	4					
		Obesity	4					
		PU/PD	4					
	Total							

*Pageat, 1995.

of anxiety while also increasing the plasticity or ability of the brain to learn a new set of reactions. This is why concurrent use of biologic agents and behavioral modification is so important. It is important that practitioners know and can explain relative side effects of all interventions involved. 'Natural' compounds are widely viewed to have fewer side effects, so owners may see these as welcome choice. Alpha-casozepine is worth studying more closely because it has the following advantages:

- Safety
  - It is a naturally occurring decapeptide, it has been classified as food, and has therefore been given GRAS (Generally Recognized As Safe) status by the FDA in a self declaration process (FDA-21 CFR §184.1553; NDI #rpt242).
- Efficacy
  - Experimental studies on rats have shown alpha-casozepine to be as efficacious as the control molecule,

Table 2 Dosing table

	Minimal Weight (kg)	Maximal Weight (kg)	Capsules A	Capsules B	Capsules C
Cat. 1	1.5	3	2		
Cat. 2	3	5		1	
Cat. 3	5	7	2	1	
Cat. 4	7	9		2	
Cat. 5	9	11	1	2	
Cat. 6	11	13			1
Cat. 7	13	15	2		1
Cat. 8	15	17		1	1
Cat. 9	17	22		2	1
Cat. 10	22	27	1		2
Cat. 11	27	32	1	1	2
Cat. 12	32	37			3
Cat. 13	37	42		1	3

diazepam, on experimental models of anxiety such as those obtained using the conditioned defensive burying (CDB) paradigm and the elevated-plus maze paradigm (Schroeder et al., 2003; Violle et al., 2006).

- Tests on healthy volunteers have shown that this substance can be used to prevent the physiologic effects of acute or chronic stress (Lanoir et al., 2002; Messaoudi et al., 2002, 2005).
- Initial studies on cats have yielded statistically significant results on the use of this molecule to control anxiety induced by social exposure (Beata et al., 2005, 2007).

Materials and methods

A multi-centre, French GCP-conducted, randomized, comparative trial was designed to compare the effects between alpha-casozepine at the daily dosage of 15 mg/kg by mouth every 24 h and the control molecule, selegiline hydrochloride at the daily dosage of 0.5 mg/kg by mouth every 24 h.

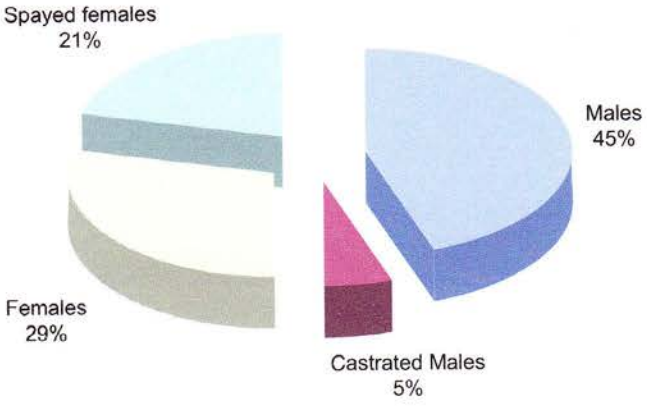

Figure 1 Sex-ratio for this study.

Selection of animals

Dogs were selected at general or referral practices. The 7 investigators were certified behaviorist surgeons with GFNVS[1] diplomas. They ensured that the dogs included in the study had not been subjected to unsuitable living conditions. Their owners wanted to have their animals treated to improve their pets' health and welfare.

Inclusion criteria

To be included, dogs had to fulfill the following 4 conditions:

- age: at least 3 months;
- weight: between 1.5 kg and 42 kg;
- diagnosis of an anxiety-related behavioral complaint; and
- EDED score above 19 at the first visit.

The emotional disorders evaluation in dogs (EDED) scale (Table 1) (Pageat, 1995) was used in the licensing application for selegiline in Europe to determine whether dogs were anxious. The EDED scale allows the practitioner to assay basic behaviors of the dog (i.e., eating, drinking, grooming, play, aggression, exploratory behavior) as well as organic signs (Marion, 2002; Pageat, 2005). The scale produces a numeric result from 9 to 45 points, with normal dogs scoring between 9 and 13. Phobic dogs score between 14 and 18, and dogs with other anxiety-related disorders score between 18 and 30.

Exclusion criteria

Dogs were excluded from the study if:

- the condition had been ongoing for less than 4 weeks;
- there was evidence that the condition was the result of illness, trauma, or organic disease (i.e., brain lesions);
- psychotropic medication or any behavioral modification has been used during the previous 2 weeks; and
- EDED score less or equal to 19.

Using these criteria 40 dogs were included in this study.

Methods

A case number was assigned to every dog that fulfilled the above requirements. This number determined what treatment would be given according to the treatment scheme (Table 2). To ensure that a blind protocol was applied, the selegiline and alpha-casozepine were packaged in 3 different kinds of capsules (25 mg, 75 mg, or 200 mg of alpha-casozepine or

[1] GFNVS means that all investigators were behaviorist veterinary surgeons graduate of French National Veterinary School diploma of behavior medicine.

0.75 mg, 2.5 mg, or 6.5 mg of selegiline hydrochloride). The treatment scheme ensured that the choice of drug was equally balanced across each weight category. The 13 categories used represent the amounts given by weight that were as close as possible to the recommended dosage (15 mg/kg for alpha-casozepine, 0.5 mg/kg for selegiline) (Table 2). Each investigator had his own randomization list. Six boxes numbered from 1 to 6 were sent to each investigator (Investigator 1 had only 4 cases). Case 1 received Product 1, Case 2 received Product 2, etc. Neither the owners nor the investigators or the supervisor(s) knew which treatment the dogs were given. Only the sponsor had access to the codes for the randomization lists. No matching was done for breed, gender, size, or across investigators.

Medications were given once daily. Clients were instructed to provide the following behavioral modification set up according to the diagnosis and the stage of the disease. This could include counter-conditioning, desensitization, communication improvement, and other interventions. There was no difference between the pattern of implemented therapies between the 2 groups.

The inclusion visit (V1) took place on Day 0 (D0). An agreement form was signed by the owner. The follow-up included 2 phone calls on D14 and D42, and 2 physical check-ups (on D28 and D56). At each follow-up contact, whether by phone or in person, the EDED scale was rated and a subjective assessment of the improvement ranging between −10 and 10 was made by the owner.

Success was defined by an EDED score becoming less than 20 **and** a final owner's assessment equal to or higher than 6/10. Effects of the 2 compounds were compared using χ^2 tests. An ANOVA was also run to assess changes across time in the EDED score and owner assessment.

Investigators also reported any adverse events and rated the probability of the potential association between the treatment and the event.

Results

Nineteen animals received each treatment.

Study population data

Age

The average age of the dogs was 49 months, with a range of 23 months to 79 months. There was no statistically significant difference in age between the alpha-casozepine group and the control group ($P = 0.12$) when data from all practitioners were lumped.

Sex

There was no sex bias: 19 males (2 of which were neutered: MC) and 19 females (9 of which were spayed: FC were) enrolled in the study (Figure 1).

Breeds and weights

The weights of the dogs enrolled ranged from 1.6 kg to 42.0 kg. The average weight was 22.2 kg. The difference in weight between the alpha-casozepine group (21.8 kg) and the selegiline group (22.6 kg) was not significant ($P = 0.84$).

Outcome of treatment

Adverse events

- Thirty-eight of 40 dogs enrolled in the study completed it. Two dogs died for reasons not associated with the

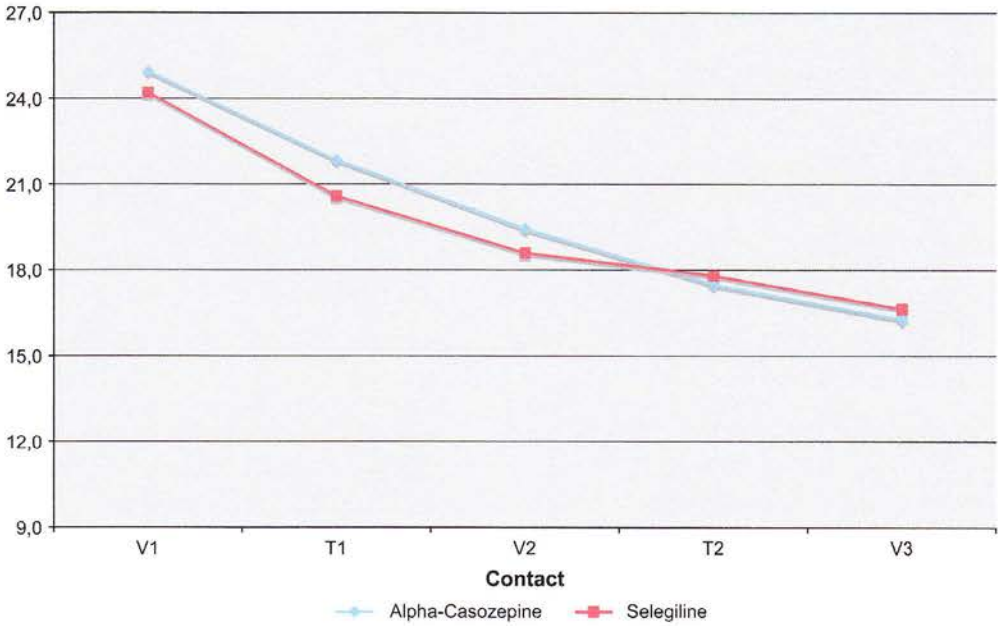

Figure 2 Comparison of global EDED scores from visits 1 through 3 for dogs treated with alpha-casozepine and selegiline.

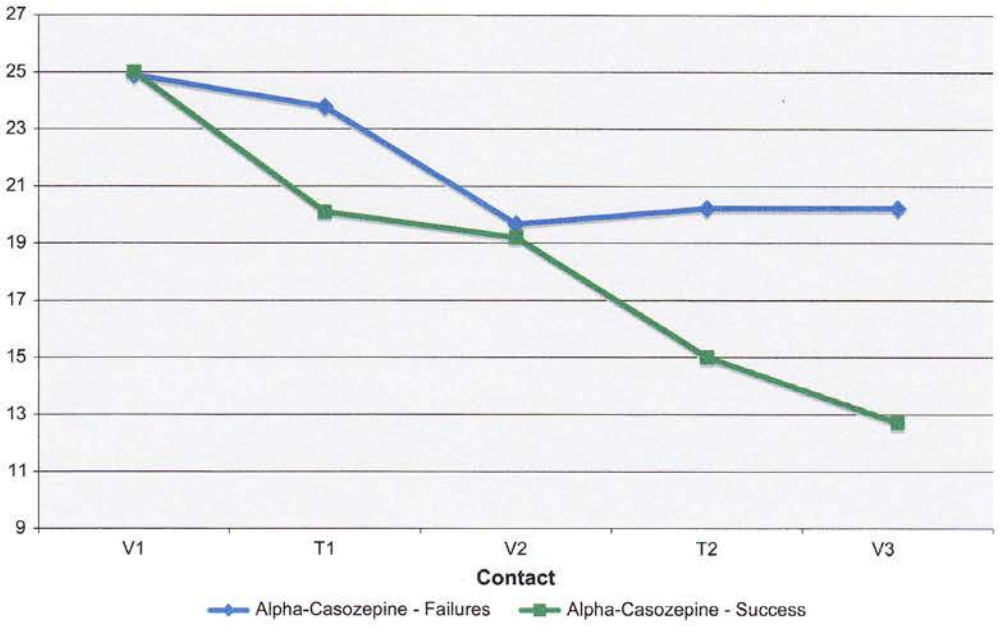

Figure 3 Comparison of average EDED scores at each visit for cases considered failures and successes when treated with alpha-casozepine.

treatment (both animals had accidents: 1 was taking alpha-casozepine, and 1, selegiline). Only 1 dog was noted to have adverse effects: 1 dog treated with selegiline exhibited cystitis. The occurrence was not suspected to be associated with treatment and the dog was treated with marbofloxacin (3 mg/kg by mouth every 24 h) for 8 days and not excluded from the study.

- This pattern of few reported side effects is consistent with toxicology data. There were no changes in the behavior of rats treated for 28 days at 40 times the recommended dosage of selegiline (600 mg/kg) and no teratogenicity or other adverse effects on weight or development of the pups with 150 mg/kg (ten times the recommended dosage) (FDA-21 CFR §184.1553; NDI #rpt242).

Successes and failures

Success was defined as follows:

- a decrease in the EDED score to below the threshold of 20; and
- owner's assessment equal to or greater than 6.

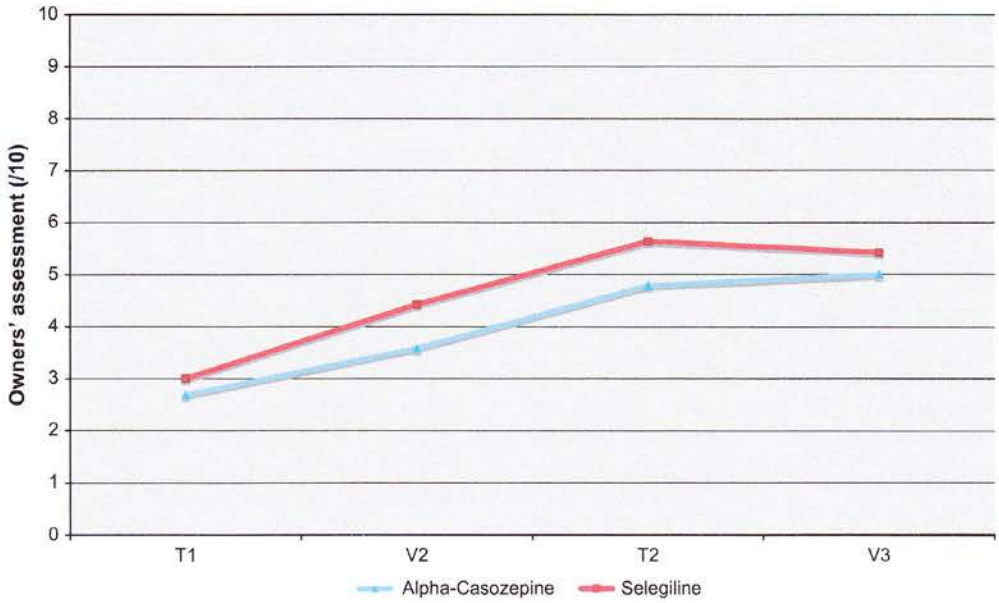

Figure 4 Comparison of owners assessment across time for dogs treated with alpha-casozepine and selegiline.

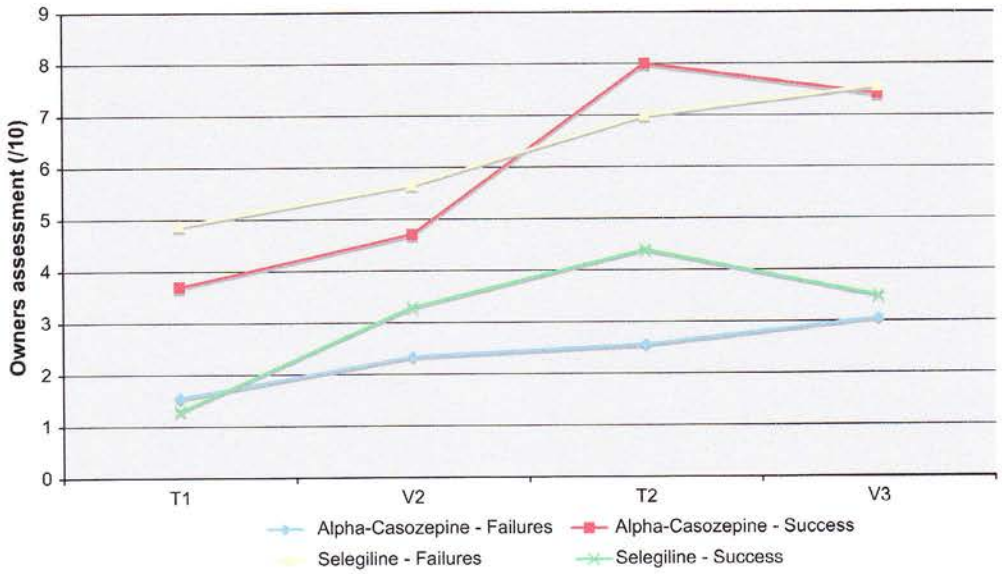

Figure 5 Comparison of owners' assessment average across the period of the study for dogs considered treatment failures and successes for each treatment group.

EDED score

Results for patients considered successes and failures when treated with alpha-casozepine or selegiline are presented in Table 3. The χ^2 test showed no significant difference between those treated with alpha-casozepine and those treated with selegiline ($P = 0.74$; $df = 1$).

Results comparing the effects of each treatment group are presented in Table 4. Both compounds were found to be effective over time. A comparison of the average decrease in the EDED score between Visits 1 and 3 (V1 vs. V3) showed a significant difference in treatment effects over time (ANOVA, $F_{(4,37)} = 47.49$; $P < 0.0001$). A similar result for the difference in EDED score between V1 and V3 was obtained for each compound analyzed separately (ANOVA $F_{(4,18)} = 22.20$; $P < 0.0001$ for alpha-casozepine; ANOVA $F_{(4,18)} = 26.33$; $P < 0.0001$ for selegiline). All EDED and owner assessment scores for all visits for the 38 dogs in the study are summarized in Table 5.

The average EDED score was slightly higher at the inclusion visit and slightly lower at the final visit in the alpha-casozepine treatment group, but these differences were not significant (Mann-Whitney U test, $P = 0.79$) (Fig. 2).

It is worth noting that no decision could be made between a satisfactory outcome and a treatment failure until D42 (Fig. 3). There seems to be an early trend indicating the onset of improvement at ~15 days, but this is not statistically significant.

Owner's assessment

Both compounds were equally efficacious when using the owners' assessments (ANOVA $F_{(3,37)} = 16.23$; $P < 0.0001$), and both compounds were equally efficacious when examined separately (ANOVA $F_{(3,18)} = 13.51$; $P < 0.0001$ for alpha-casozepine; ANOVA $F_{(3,18)} = 5.96$; $P = 0.01$ for selegiline). There was no significant difference between the 2 products in terms of the owner's assessment at V3-D56 (Mann-Whitney U test, $P = 0.73$) (Fig. 4). When comparing owner opinions of success and failure the slopes of the response for each compound are different, but the final points overlap (Fig. 5).

Investigator effect

Because of the small number of cases seen by each investigator it was impossible to accurately test for any inter-investigator differences or effects. That said, as discussed, the average combined or lumped scores did not

Table 3 Successes and failures for dogs in each treatment according to outcome criteria

	Successes	Failures
Alpha-casozepine	10	9
Selegiline	9	10

Table 4 Comparison of EDED scores and owners' assessments during the study by treatment group

	EDED on D0	EDED on D56	Owner's assessment on D14	Owner's assessment on D56
Average	24.6	16.4	2.8	4.8
Alpha-casozepine	25.0	16.3	2.7	5.3
Selegiline	24.2	16.6	3.0	5.4

D, day; EDED, emotional disorders evaluation in dogs.

Table 5 List of cases

	V1	T1		V2		T2		V3			
	EDED	Eval.	EDED	Eval.	EDED	Eval.	EDED	Eval.	EDED	Result	Product
01	25	1.0	25	2.0	20	2.0	18	5.0	20	Failure	Alpha-casozepine
02	21	5.0	20	4.0	20	5.0	20	6.5	21	Failure	Alpha-casozepine
03	20	3.0	20	5.0	11	2.0	23	2.0	23	Failure	Alpha-casozepine
04	28	0.0	28	2.0	21	4.0	18	5.0	16	Failure	Alpha-casozepine
05	21	2.0	19	3.0	16	2.0	16	0.0	20	Failure	Alpha-casozepine
06	23	1.0	23	0.0	19	2.0	19	3.0	20	Failure	Alpha-casozepine
07	30	1.0	28	2.0	21	3.0	21	4.0	20	Failure	Alpha-casozepine
08	28	1.0	23	5.0	19	3.0	19	2.0	14	Failure	Alpha-casozepine
09	28	0.0	28	−2.0	30	0.0	28	0.0	28	Failure	Alpha-casozepine
10	23	5.0	20	7.0	18	9.0	8	8.0	9	Success	Alpha-casozepine
11	20	2.0	14	3.0	11	6.0	11	7.0	9	Success	Alpha-casozepine
12	25	7.0	11	6.0	16	8.0	13	8.0	12	Success	Alpha-casozepine
13	28	0.0	28	5.0	24	8.0	16	9.0	12	Success	Alpha-casozepine
14	26	2.0	22	3.0	22	5.0	22	6.0	15	Success	Alpha-casozepine
15	23	6.0	16	5.0	19	6.0	16	7.0	16	Success	Alpha-casozepine
16	25	6.0	19	6.0	19	7.0	16	8.0	13	Success	Alpha-casozepine
17	23	5.0	15	6.0	14	7.0	11	7.0	11	Success	Alpha-casozepine
18	26	3.0	26	5.0	22	7.0	16	8.0	16	Success	Alpha-casozepine
19	31	1.0	30	1.0	27	5.0	21	6.0	14	Success	Alpha-casozepine
20	20	2.0	20	0.0	20	0.0	20	0.0	20	Failure	Selegiline hydrochloride
21	22	1.0	17	3.0	17	4.0	17	5.0	14	Failure	Selegiline hydrochloride
22	28	2.0	24	4.0	19	4.0	23	5.0	20	Failure	Selegiline hydrochloride
23	27	2.0	20	2.0	17	2.0	24	5.0	24	Failure	Selegiline hydrochloride
24	22	0.0	19	0.0	18	0.0	18	0.0	19	Failure	Selegiline hydrochloride
25	28	0.0	28	5.0	26	6.0	21	6.0	21	Failure	Selegiline hydrochloride
26	20	5.0	20	6.0	19	6.0	20	6.0	22	Failure	Selegiline hydrochloride
27	24	−7.0	23	5.0	23	8.0	21	8.0	20	Failure	Selegiline hydrochloride
28	28	2.0	28	2.0	29	5.0	21	−5.0	14	Failure	Selegiline hydrochloride
29	29	6.0	21	6.0	21	9.0	19	5.0	19	Failure	Selegiline hydrochloride
30	26	6.0	19	5.0	17	6.0	15	7.0	15	Success	Selegiline hydrochloride
31	25	8.0	18	9.0	18	10.0	19	8.0	18	Success	Selegiline hydrochloride
32	23	5.0	23	5.0	19	6.0	17	8.0	16	Success	Selegiline hydrochloride
33	23	6.0	14	7.0	12	8.0	12	9.0	12	Success	Selegiline hydrochloride
34	23	3.0	23	4.0	19	5.0	15	6.0	12	Success	Selegiline hydrochloride
35	21	3.0	19	3.0	15	7.0	15	8.0	15	Success	Selegiline hydrochloride
36	22	5.0	19	6.0	17	7.0	12	7.0	11	Success	Selegiline hydrochloride
37	27	5.0	21	6.0	15	6.0	17	6.0	13	Success	Selegiline hydrochloride
38	22	3.0	15	6.0	12	8.0	12	9.0	11	Success	Selegiline hydrochloride
Average	24.6	2.8	21.2	4.0	18.9	5.2	17.6	5.4	16.4		

EDED, emotional disorders evaluation in dogs.

differ, so such effects should be consistent between the treatment groups.

Conclusion

Alpha-casozepine, a non-pharmaceutical compound, seems to be effective in treating anxiety in dogs and other species suffering from anxiety-related conditions (Beata et al., 2005; Violle et al., 2006). In this blinded study, the effects of treatment with selegiline and alpha-casozepine were shown to be equally effective.

For clients who worry about any potential side effects, the GRAS status of alpha-casozepine may provide reassurance. In this study, we had no adverse effect that is consistent with toxicology data.

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ERRATUM

In the May/June issue of the Journal of Veterinary Behavior: Clinical Applications and Research (Volume 2, Issue 3), Dr. Claudia Edwards was erroneously excluded from the author list of the following article: Heiblum, A., Labastida, R., Chavez Gris, G., Tejeda, A., 2007. "Didy," a clinical case of cognitive dysfunction syndrome. J. Vet. Behav.: Clin. Appl. Res. 2, 68-72.

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