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Research

An open-label prospective study of the use of L-theanine (Anxitane) in storm-sensitive client-owned dogs

Amy L. Pike ^{a,b,*}, Debra F. Horwitz ^b, Heidi Lobprise ^{c,d}^a Veterinary Behavior Solutions, Louisville, Kentucky^b Veterinary Behavior Consultations, St. Louis, Missouri^c Main Street Veterinary Hospital, Fort Worth, Texas^d Virbac Animal Health, Fort Worth, Texas

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ABSTRACT

There is a growing interest in veterinary medicine toward the use of alternative treatments including nutraceuticals. This open-label trial evaluated the use of the nutraceutical L-theanine (Anxitane, Virbac Animal Health, Fort Worth, TX) (N-ethyl-L-glutamine) in client-owned dogs with a history of storm sensitivity. Dogs had to be between 1 and 8 years and were recruited from general practices in the study area. All enrolled dogs were healthy based on physical examination and laboratory analysis and not currently being treated for any chronic medical or behavioral disorder. Owners completed a questionnaire for the initial storm. Then, after starting the test article, owners completed the same questionnaire for each of 5 subsequent storms. Questionnaires evaluated 11 individual behavior manifestations of storm sensitivity using a 0–5 Likert scale. Storm severity was also rated on a 0–5 Likert scale. At the end of each storm, owners evaluated time to return to the patient's normal baseline behavioral state. Owners were given a standardized protocol of environment and behavior management, but no other behavior modification was prescribed. Eighteen dogs completed the trial and were available for statistical analysis. There was a statistically significant decrease ($P < 0.0001$) in global anxiety scores from baseline to exit evaluation. Additionally, time to return to baseline normal scores demonstrated a significant decrease ($P = 0.0063$) from baseline storm to last storm evaluated. Treatment success was achieved for the behaviors of drooling (83.33%), following people (75%), panting (76.47%), pacing (78.57%), and hiding (78.57%). Owner satisfaction with treatment was 94% (17 of 18). This study suggests that L-theanine can be an effective treatment for storm sensitivity, decreasing severity of the dog's overall response, time for the dog to return to baseline after storm ends, and diminishing drooling, following people, pacing, panting, and hiding.

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Introduction

Noise sensitivities and phobias in dogs are common behavioral disorders presented to veterinarians in general practice and as behavioral referrals (McCobb et al., 2001; Bamberger and Houp, 2006; Gazzano et al., 2008; Denenberg et al., 2013). Numerous terms for storm sensitivity are used interchangeably throughout the literature (McCobb et al., 2001; Bamberger and Houp, 2006; Gazzano et al., 2008; Denenberg et al., 2013), including aversion, fear, anxiety, reactivity, sensitivity, and phobia. In this article, the term storm sensitivity is used operationally to refer to the group of

clinical behaviors and physiological signs that dogs may exhibit during a storm. Although storm sensitivities are a frequent complaint among owners, veterinary practitioners may still lack important information on the types and severity of symptoms and the safest and most effective treatment interventions.

Most information to date on the prevalence of symptoms has been compiled from Internet surveys. A 2013 Internet survey of 1201 dog owners (single and multidog homes) sought to determine the prevalence of behavior problems in the surveyed population (Denenberg et al., 2013). Of the 1960 dogs surveyed, 577 (29.4%) exhibited fear or anxiety. Noise aversions were equally common, 17% of the 577 dogs displayed some category of noise aversion. Thunderstorm sensitivity was the most common form of noise aversion reported with 84 (86% of the total 17% noise aversive dogs) showing signs during storms (Denenberg et al., 2013). A 2001

* Address for reprint requests and correspondence: Amy L. Pike, DVM, Veterinary Behavior Solutions, PO Box 1544, Mt Washington, KY 40047. Tel: +1-888-502-0223x1.
E-mail address: amypikedvm@gmail.com (A.L. Pike).

Internet survey focused only on thunderstorm-phobic dogs in an attempt to identify predispositions, signs, and progression of canine thunderstorm phobia (McCobb et al., 2001). More than two-thirds of the 69 subject dogs (68%) displayed 1 or more physical symptoms during a thunderstorm, including panting, shaking, loss of bladder or bowel control, and salivation (McCobb et al., 2001). Hiding was prevalent among surveyed dogs with 57% showing hiding behavior, and the bathroom was the preferred location for 49% of those dogs. Attention-seeking behaviors were also prevalent, with 42% of the dogs pawing at the owners or following them around the house (McCobb et al., 2001).

Laboratory and clinical studies on treatment modalities for noise sensitivities have been conducted on behavior modification (Crowell-Davis et al., 2003; Levine et al., 2007), homeopathic preparations (Cracknell and Mills, 2008), botanical extracts (Deporter et al., 2012), body wraps (Cottam and Dodman, 2009; Cottam et al., 2013), and pheromones (Sheppard and Mills, 2003; Levine et al., 2007). Anecdotally, veterinarians have prescribed conventional and readily accessible sedatives or tranquilizers, commonly acepromazine, which is familiar to many practitioners and found in many veterinary pharmacies. Acepromazine is a phenothiazine neuroleptic agent that acts by blocking postsynaptic dopamine receptors in the central nervous system, inhibiting the release of and increasing the turnover rate of dopamine (Plumb, 2011). As a tranquilizing agent, phenothiazines are very dependent on dose to achieve anxiolytic properties, often resulting in a large degree of sedation, which clients may find unacceptable and lead them to discontinue using the prescription. Over time, research data on anxiolytic medications have broadened, giving the veterinary practitioner other more efficacious options, such as tricyclic antidepressants (TCAs) (Crowell-Davis et al., 2003), benzodiazepines (Crowell-Davis et al., 2003; Herron et al., 2008; Ibanez and Anzola, 2009), alpha-2 agonists (Ogata and Dodman, 2011), selective serotonin reuptake inhibitors (SSRIs) (Ibanez and Anzola, 2009), and serotonin 2A antagonist/reuptake inhibitors (Gruen and Sherman, 2008).

Across veterinary disciplines, there is interest in the use of alternative treatment modalities, including acupuncture (Jianzhu et al., 2007; Sanchez-Araujo and Puchi, 2011; Kidd, 2012), homeopathy (Chapman, 2011; Neumann et al., 2011; Kidd, 2012), and nutraceuticals (Gingerich and Strobel, 2003) for the treatment of common medical and behavioral disorders (Wells, 2006; Araujo et al., 2008; Araujo et al., 2012; Kato et al., 2012). Owners often perceive that these options are safer with fewer side effects, but comparison studies have not been done to verify that assertion. Until recently, little data existed outside a laboratory setting of the efficacy of nutraceuticals for storm sensitivities in the canine patient (Berteselli and Michelazzi, 2007; Deporter et al., 2012).

L-theanine (Anxitane, Virbac Animal Health, Fort Worth, TX) (*N*-ethyl-L-glutamine), an amino acid found in green tea, is structurally similar to glutamic acid and increases the inhibitory neurotransmitter gamma-aminobutyric acid along with serotonin and dopamine levels in the brain (Nathan et al., 2006). Studies in animals have shown peak concentrations in the blood and liver 1 hour after administration and 5 hours after administration in the central nervous system. Both concentrations decline over a 24-hour period (Nathan et al., 2006). Two data-based presentations and abstracts have shown L-theanine to be effective in dogs to decrease fear of strangers (Araujo et al., 2010) and decrease anxiety in cats (Dramard et al., 2007). There are currently no studies that demonstrate statistically significant data on the use of L-theanine for thunderstorm sensitivities in dogs (Berteselli and Michelazzi, 2007). The objective of the present study was to test whether a nutraceutical intervention containing L-theanine could provide safe and effective relief for signs of anxiety for client-owned storm-sensitive dogs.

Materials and methods

Test article

Anxitane tablets are a nutraceutical supplement composed of a 99.95% pure active L-isomer form of theanine. The test article (Anxitane) is formulated as a flavored chewable tablet in 50 mg (Anxitane S [small]) or 100 mg (Anxitane ML [medium/large]) size that is scored for dosing administration. Each dog received the labeled dosage; 25 mg (1 half tablet of Anxitane S) by mouth twice daily for dogs weighing up to 10 kg, 50 mg (1 half tablet of Anxitane ML) by mouth twice daily for dogs more than 10 kg and up to 25 kg, or 100 mg (1 full tablet of Anxitane ML) by mouth twice daily for dogs weighing more than 25 kg. The twice daily dose was given for at least 4 weeks or until at least 5 recordable thunderstorms were experienced while on the test article.

Study design

The study was a 1-group, multicenter with a single investigator, open-label, prospective clinical trial conducted in accordance with Center for Veterinary Medicine's Good Clinical Practice Guideline #85, VICH GL9, June 8, 2011.

Subjects

Dogs were recruited from 4 St. Louis Missouri and Metro East Illinois area general practices in the spring of 2013. Participating clinics and practitioners were solicited based on a professional relationship with the primary investigator and specifically chosen for their large client population and geographic diversity across the study area. Clinicians recruited subjects using advertising on social media, Web site, and posted signs in the clinic several months before the targeted storm season. Test subjects were enrolled if they met all the inclusion criteria (Table 1) or were prohibited from participation if they met any of the exclusion criteria (Table 2).

The primary care veterinarian performed physical examinations on potential subject dogs and collected blood for laboratory analysis. Once the primary care clinician deemed the subject healthy for enrollment, the primary investigator conducted a telephone interview with the client to further verify that the enrollment criteria were met and to rule out any concurrent significant additional behavioral diagnosis including severe phobic responses that might compromise animal welfare if left without appropriate treatment. All patients with laboratory results (complete blood count, general chemistry profile, and total T4) significantly outside the laboratory given reference range values were deemed ineligible. The investigator initially interviewed a total of 34 dogs. Seven were disqualified during the intake interview; 1 was excluded for short

Table 1
Inclusion criteria for subject dogs

- Older than 1 year, younger than 9 years (1 through 8 inclusive)
- Either sex, intact or neutered
- Not pregnant or lactating
- Any breed, known or unknown
- Client owned for at least the past 12 months, with available medical records from primary care veterinarian
- Display at least 3 behaviors from the given symptom list during a thunderstorm
- Have shown reactivity to thunderstorms for at least the 2 previous thunderstorm seasons
- Physical examination within normal limits
- Complete blood count, chemistry panel, and total T4 results within given reference value ranges

Table 2

Exclusion criteria for subject dogs

- Chronic medical problems noted by medical records, physical examination, or laboratory analysis
- Concurrent diagnosis of separation anxiety, cognitive dysfunction, or obsessive compulsive/compulsive disorder
- Displaying aggression that prohibited examination or venipuncture
- Treatment with psychotropic, anxiolytic, or sedative medications within 2 weeks of starting the trial or for more than 14 days during a previous thunderstorm season

duration of ownership and no known history; 1 was excluded for a significant recurrent behavioral diagnosis (separation anxiety); 4 were excluded for exceeding the 8-year age limit; and 1 was excluded because of current administration of daily fluoxetine hydrochloride. One subject was excluded based on abnormal serum chemistry results.

Of the 26 qualified patients, 2 withdrew early from the study; 1 owner withdrew for personal reasons (pregnancy) and 1 dog demonstrated signs consistent with worsening anxiety on the first storm after the first dose of the test article was given and the owner opted to withdraw from the study. Three owners failed to return their paperwork at the termination of the study despite multiple attempts to contact them via phone and electronic mail. Three patients were excluded in the statistical evaluation; 1 for having only completed two storms and two for providing incomplete or multiple entries. A total of 18 owners completed the questionnaire for all 5 required storms (Table 3).

Data collection

During initial telephone behavioral screening interview, owners were asked to rate their dog's global storm sensitivity using a 0–5 Likert scale. These scores were based on subjective owner assessment and not based on a trained investigators' definition of severity. The goal was to allow the owners to use their own rating system throughout the trial. On enrollment, owners received a binder with all necessary study paperwork and were required to complete the baseline storm evaluation for the first storm experienced without the test article. Study questionnaires evaluated 13 individual behavior manifestations of storm responses (Table 4) using a 0–5 Likert scale. Storm severity was rated using a 0–5 Likert scale for rain, wind, thunder, lightning, and hail. Official tornado warnings (siren) experienced during the storm were dichotomized

Table 4

Symptoms and definitions of storm sensitivity

- Panting**—breathing through the mouth; tongue not contained inside mouth cavity; generally excessive and not related to any physical exertion
- Pacing**—aimlessly walking back and forth; inability to lie down when prompted
- Following**—desire to be near humans at all times; right under foot
- Hiding**—purposefully seeking out isolated areas of the house; located under furniture or inside small confined areas; inability for owners to find pet
- House soiling**—urination or defecation indoors (unless otherwise trained to do so; or unless previously not considered house trained)
- Trembling**—shaking; shivering; full body or extremity only
- Drooling**—excessive salivation; not related to recent water consumption
- Destruction**—purposefully damaging items not meant for this purpose (i.e., not toys or bones)
- Vocalization**—whining, barking, crying, howling outside normal behavior; not directed at normal triggers, such as strangers, other animals, or seeking owner attention to basic needs
- Increased vigilance**—on the alert; highly aroused; attentive and watchful
- Vomiting**—involuntarily ejecting stomach contents through the mouth
- Escape behavior**—attempts made to get out, break away, or flee from confinement or enclosure (including from home)
- Defensive aggression**—Growling, snarling, snapping, nipping, or biting the owners if attempts are made to interact with the dog, restrain, or attempt to stop any of the aforementioned behaviors (NOTE: for safety reasons, do NOT purposefully attempt to elicit this behavior; if your pet is displaying this behavior, attempt should be made to safely isolate the pet)

to yes or no and recorded. Additionally, clients evaluated the time it took the dog to return to normal baseline behavioral state at the conclusion of each storm. Categories provided for this evaluation were as follows: less than 10 minutes, 10–20 minutes, 30 minutes–1 hour, or longer than 1 hour. Owners were also given a standardized environmental protocol that they were allowed to follow if the dog was willing and able (Table 5) but were not required to record which procedures they did or did not follow during each storm. The investigators felt that these were common procedures already available to the owners via other sources (Internet and others), and the investigators wished to avoid the owner using punishment in any way. Additionally, increased record keeping may lead to participant attrition from the study, which the investigators wished to avoid.

After the baseline thunderstorm was recorded, the owner began administration of the test article according to the labeled dose (see previous data). Owners completed a thunderstorm evaluation identical to the baseline storm evaluation for each storm experienced. Owners only evaluated storms for which they were

Table 3

Subject demographic data

Case no.	Age (y)	Sex	Neutered	Breed	Source	Attended puppy socialization	Favorite hiding place
B-211	6	Female	Spayed	Labrador retriever/Border collie mix	Rescue	Yes	Office
C-221	8	Female	Spayed	Labrador retriever/Greyhound mix	Rescue	No	None
C-222	2	Male	Castrated	Labrador retriever/Coonhound mix	Rescue	No	Kennel
C-225	8	Female	Spayed	Rat terrier mix	Rescue	No	Bathroom
C-226	8	Female	Spayed	Schipperke	Breeder	Yes	Owner bed
C-228	5	Female	Spayed	Beagle/Border collie mix	Rescue	No	None
C-229	8	Female	Spayed	Golden retriever	Rescue	Yes	Kennel
C-230	8	Male	Castrated	Chesapeake Bay retriever	Rescue	Yes	Basement
D-231	8	Male	Castrated	Shih tzu	Friend	No	None
D-233	2	Female	Spayed	Lakeland terrier	Breeder	No	None
D-234	2	Female	Spayed	Lakeland terrier	Breeder	No	Bathroom
E-242	8	Male	Castrated	Bloodhound	Rescue	No	Owner bed
E-247	2	Female	Spayed	Chocolate Labrador	Rescue	No	Closet
E-248	8	Female	Spayed	Rat terrier	Friend	No	Owner bed
E-250	3	Male	Castrated	Shih tzu/Brussels griffon mix	Rescue	No	Bathroom
E-253	5	Male	Castrated	Yellow Labrador	Stray	No	Closet
V-302	7	Female	Spayed	Shih tzu	Rescue	No	None
V-303	5	Female	Spayed	Dachshund/Beagle mix	Rescue	No	None

Table 5
Standardized environmental protocol

- You may place your dog in a darkened room, preferably an interior one with no windows or ones that are darkened using blackout curtains.
- You may place the dog in a crate if the dog is kennel trained and will willingly enter it during a storm without being forced. If your dog shows any distress while crated during a storm, remove it immediately and do not use a crate when you are not home
- You may play white noise, such as a loud fan or music, to drown out the ambient noise of the storm
- Try to avoid interacting with your dog when they are showing anxious and clingy behaviors. If your pet enjoys and calms while lying next to you during storms, then allow them to do so
- You are not allowed to use any punishment, including verbal admonishment, physical reprimands (spanking), or use of punishment devices including shock collars or shaker cans
- You may attempt to busy yourself with other things (reading, watching TV, or hobbies) during a storm event to facilitate ignoring the pet and not fostering the nervous behavior
- If your dog enjoys playing certain games or training, you may try using these activities as a distraction and to form a more pleasant association with the event
- If your dog will eat during a storm and is not aggressive with food-stuffed toys, you can try distracting your pet with 1 of those items

physically present with the test subject for the duration of the storm. To be eligible for data analysis, the patient must have experienced at least 5 storms while on the test article during a minimum of 4 weeks (maximum of 8 weeks). At the conclusion of the requisite period, owners completed the exit evaluation, assessing which behavior symptoms improved during the trial, the patient's global storm sensitivity level at the end of the trial, their overall satisfaction with the test article, and their likelihood of using the product in the future.

Statistical analysis

Each sign was evaluated individually across all patients for percentage success using a simple ratio. Success was defined as an improvement in the specific behavior score following the 5th storm as compared with a baseline score of that behavior. Behaviors scored as 0 at baseline were not included in the assessment of success for that behavior. A 95% confidence interval was constructed.

Before the administration of the test article and at exit evaluation, the owner assigned a global storm sensitivity score. The exit score compared with baseline was tested for significance of change using a sign test.

The time it took for the pet to return to normal baseline behavioral state was dichotomized across 4 categories, and the change from baseline was calculated using a sign test.

Treatment effects were evaluated using a 2-sided test with alpha = 0.05. Treatment success (yes or no) was evaluated based on the behavior scores from the baseline behavior questionnaire and the behavior scores from the last thunderstorm behavior questionnaire. Where behavior scores at baseline are greater than 0, the change from baseline was calculated. When at least 50% of these scores improved by at least 1 rating level, and none of these scores worsened, the dog was considered a treatment success. Dogs that did not meet this criterion were considered treatment failures. The success rate was calculated, and a 95% confidence interval was constructed (the frequency procedure in SAS, SAS Institute, Inc, Cary, NC). When the lower bound of the confidence interval exceeded 0, treatment effectiveness was concluded.

To account for storm differences, summed behavior scores were assessed using a paired *t* test from baseline to final storm using a global correction score for the storm severity. This global correction

score is the average of Likert ratings on each parameter. Additionally, the summed behavior scores were assessed from baseline to final storm using the global correction score for storm severity multiplied by a factor of 1.5 if there was a tornado warning present to take into account the increased pet owner stress and need to move into safe shelter.

End of study outcomes from the owner exit questionnaire were statistically analyzed. The change in global severity score at exit versus baseline was calculated for each dog. Results were analyzed using a sign test for paired data (the UNIVARIATE procedure in SAS). Overall improvement scores were compiled as 'mild', 'moderate', and 'greatly improved' versus 'no change'. Satisfactory levels were 'not at all satisfied', 'somewhat unsatisfied', 'neutral', 'somewhat satisfied' and 'very satisfied'. Likely to continue scores were compiled as 'not at all likely', 'somewhat unlikely', 'neutral', 'somewhat unlikely' and 'very likely'. The proportion of owners responding positively was calculated, and a 95% confidence interval was constructed. When the lower bound of this interval exceeded 0, treatment effectiveness was concluded.

Results

Demographic data

Among the 18 dogs used in statistical analysis, 12 were females (12 of 18; 67%), 6 were males (6 of 18; 33%), and all 18 were spayed or neutered. The ages ranged from 2 to 8 years with a mean age of 6. There were 7 purebred or mixed breed dogs representing the sporting group (39%), 5 (28%) representing hounds or hound mixes, 4 terrier or terrier mixes (22%), 3 toy or toy breed mixes (17%), two herding breed or mixes (11%), and 1 nonsporting breed (6%). There were 4 mixed breed dogs that crossed over 2 distinctly different breed groups and were included in the total for each category. Of the 18 dogs, 1 (6%) the owners obtained as a stray dog, 2 (11%) had been obtained from a friend, 3 were purchased from a breeder (17%), and most of them (12 of 18; 67%) had been adopted from a rescue organization. Of the 12 dogs that showed a preference for a hiding location during a storm, 3 (25%) went into the bathroom, 3 (25%) hid in or under the owner's bed, 2 (17%) hid in a kennel, 2 (17%) sought to hide in a closet, 1 (1%) went to the basement, and 1 (1%) hid in another room (office). Only 4 of the test subjects had a known history of attending puppy socialization classes. All 18 dogs included in final analysis experienced more than 5 storms during the treatment period.

Treatment data

Behavior signs that demonstrated a high rate of treatment success in the test subjects as to criterion described earlier include drooling (83.33%), following people (75%), panting (76.47%), pacing (78.57%), and hiding (78.57%) (Figure 1; Table 6).

The global storm sensitivity score from the intake telephone interview and exit evaluation were assessed for change in their value. Intake global scores ranged from 3 to 5, with a mode of 4. The 18 dogs available for final analysis experienced a statistically significant decrease ($P < 0.0001$) in their global storm sensitivity scores with a median decrease of 2 points on the 5-point Likert scale (Table 7).

The time required for the patient to return to baseline normal behavioral state was evaluated for change from the baseline storm to the final recorded storm. These scores demonstrated a significant decrease ($P = 0.0063$) with a median decrease of 1 category (Table 7).

Because storm intensity and/or quality could affect a dog's reaction for each individual storm experienced, an attempt was made

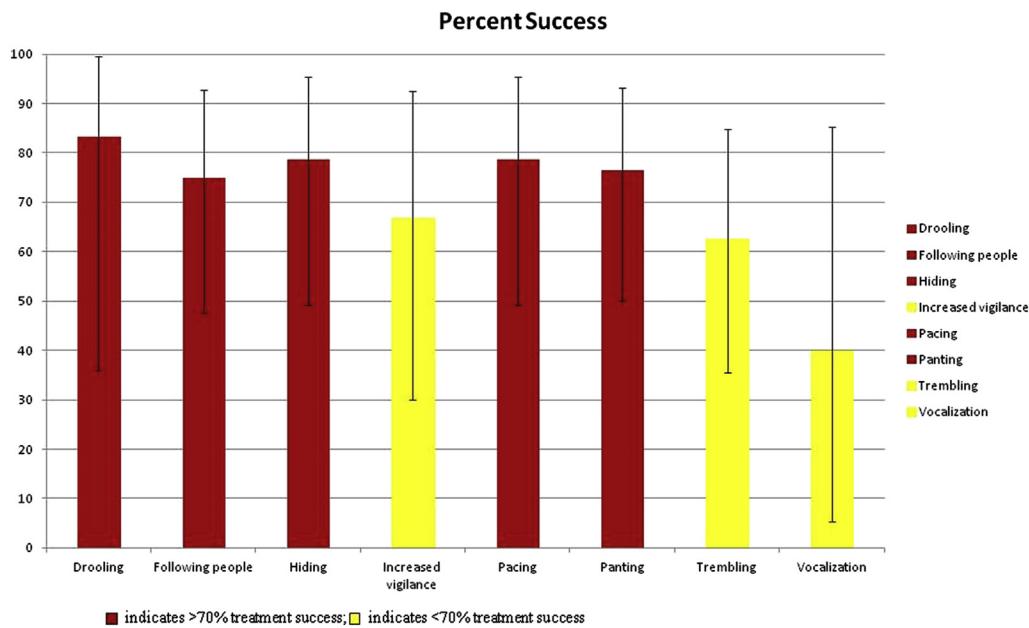


Figure 1. Percent success for individual symptoms.

to verify that the character of the storms experienced did not affect the results obtained. The summed behavior score for each dog was divided by the global correction score and then compared with both the 5th thunderstorm completed and the last thunderstorm recorded. To account for the possibility of additional stress that both the owner and patient experienced during a tornado warning, the global correction score was multiplied by a factor of 1.5 where applicable and compared with both the 5th thunderstorm and the last thunderstorm recorded. Using a paired *t* test, a *P* value of <0.0001 was obtained for all categories, indicating that storm intensity and/or quality did not impact the results obtained (Figure 2; Table 8).

Overall treatment success using the designated criteria was achieved in 12 of the 18 dogs (Figure 3, green; Table 9).

Owner satisfaction data were collected and analyzed from the exit evaluation. Seventeen of the 18 owners (94.44%) saw overall positive improvement in their pet, were satisfied with the product, and would continue using the test article if given the opportunity (Figure 3, blue; Table 9).

Discussion

Results of this study indicate that L-theanine may be beneficial in providing relief from the intensity of signs dogs most commonly experience during a thunderstorm. Most subject owners reported 5 symptoms (Table 6): following people (16 of 18; 89%), panting (17 of 18; 94%), trembling (16 of 18; 89%), hiding (14 of 18; 78%), and

pacing (14 of 18; 78%). These data are consistent with the findings of McCobb et al. that commonly reported physical and behavioral symptoms are observed in dogs during storms (McCobb et al., 2001). For 4 of these most commonly reported symptoms, following people, hiding, panting, and pacing, more than 75% of subjects experienced clinical improvement of at least 1 point on the Likert scale while being treated with the test article. Additionally, more than half (10 of 16; 63%) of the subjects that trembled experienced improvement of at least 1 point on the Likert scale. By prescribing L-theanine, the veterinary practitioner may have the ability to diminish the intensity of some of the most commonly reported signs in a high percentage of patients suffering from their reactions to storms.

Situational anxieties such as those associated with storms can manifest as a variety of clinical signs in each individual patient. To better compare the overall anxiety experienced across the entire patient population, a global score of severity is often assigned during clinical trials to get a better assessment of improvement or deterioration (Crowell-Davis et al., 2003). During the intake interview with the primary investigator, owners were asked to rank their dog's overall anxiety during thunderstorms, which was then compared with the exit evaluation. Global scores showed a median decrease of 2 points on the 5-point Likert scale.

The time it takes a dog to return to a normal baseline state of behavior is clinically relevant to the owners, especially when storms occur at night. The significant change from baseline seen in the present study may be an indication of how fast the pet will return to a state of somnolence after a storm has ended when using the test product.

One important feature of the present study is the use of naturally occurring thunderstorms versus those artificially produced in a laboratory setting. To ensure there was no treatment effect

Table 6
Summary of the assessment of individual behaviors displayed

Item	N	Percent success	95% Confidence interval
Drooling	6	83.33	35.88, 99.58
Following people	16	75.00	47.62, 92.73
Hiding	14	78.57	49.20, 95.34
Increased vigilance	9	66.67	29.93, 92.51
Pacing	14	78.57	49.20, 95.34
Panting	17	76.47	50.10, 93.19
Trembling	16	62.50	35.43, 84.80
Vocalization	5	40.00	5.27, 85.34

Table 7
Summary of the assessment of global severity and time to calm

Item	Median decrease	P value
Severity (change from baseline)	-2.00	<0.0001
Time to calm (change from baseline)	-1.00	0.0063

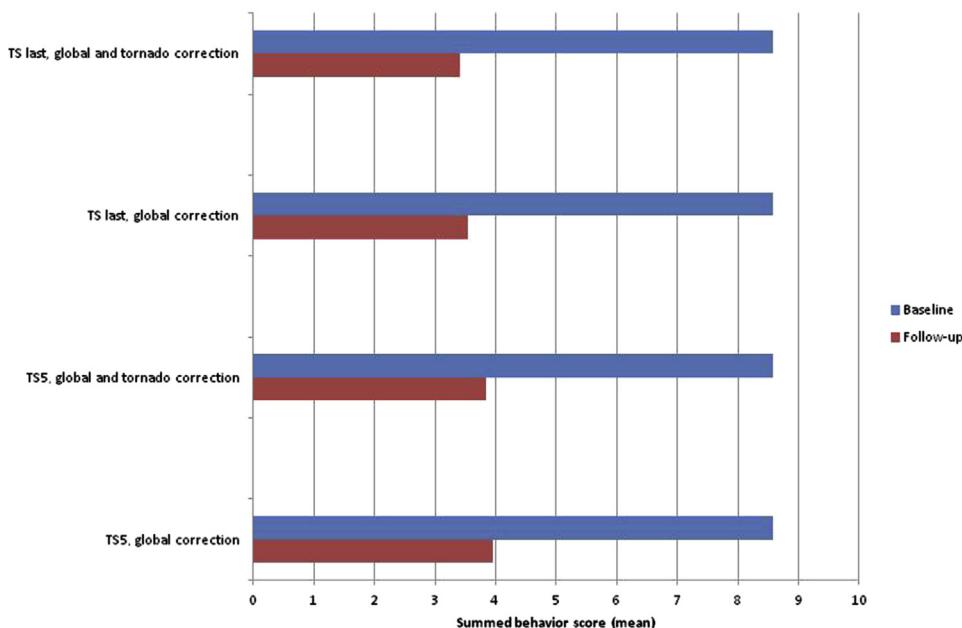


Figure 2. Baseline and follow-up summed behavior score (mean) for the last experienced thunderstorm (TS last) with global storm score correction (with and without tornado warning correction factor) and the fifth experienced thunderstorm (TS5) with global score correction (with and without tornado correction factor).

produced as a result of diminishing thunderstorm intensity through the trial, a storm global score was applied to each storm, both with and without a tornado warning factor of 1.5 where applicable (Figure 2; Table 8). The outcomes indicate that the present study was not affected by the quality or intensity of the storm itself.

This study used owner self-reporting to gather the data for analysis similar to other clinical pharmaceutical trials (Ibanez and Anzola, 2009; Ogata and Dodman, 2011; Denenberg et al., 2013), but every attempt was made to mitigate the potentially subjective nature of owner reporting. Owners were provided with a standardized definition list of each behavior sign to minimize possible differences in interpretation. By collecting baseline storm evaluation data before starting the test article, each dog acted as its own control subject and data were analyzed based on the differences from baseline. Additionally, 1 owner was designated as the evaluator per subject home.

This study was an open-label trial, and owners were self-selected to participate in the trial, which may have lead to over-reporting of clinical efficacy because of the placebo effect (McMillan, 1999). A 2008 double-blind placebo-controlled study conducted on a homeopathic remedy for noise phobias reported a 50% therapeutic effect because of the placebo effect alone (Cracknell and Mills, 2008). A placebo effect has also been reported

for tests of pharmaceutical agents for separation anxiety (Landsberg et al., 2008). A limitation of the present study is the lack of a placebo control group. Future research should include placebo-controlled, double-blinded tests of L-theanine for the treatment of reactions to storms. Further research is warranted to validate the results obtained versus a trial with a test article and placebo administration.

The present study attempted to standardize the environments across patients and reduce the number of potential variables effecting results. Owners were given a list of environmental procedures that were and were not permissible (Table 5) but were not required to record which procedures they did or did not follow during each storm. The lack of recording of the environmental procedures does not allow us to determine if differences in environmental management play a role in the success seen with the product, an acknowledged weakness in the data. However, the recommendation of behavioral and environmental procedures without recording their use is comparable to other clinical trials that combine medication, behavior modification, and management

Table 8

Summary of the assessment of study outcomes—change from baseline in the summed behavior scores corrected for global and global + tornado warning values

Item	Baseline mean	Follow-up mean	Change from baseline	Standard deviation	P value ^a
TS5, global correction	8.58 ^b	3.96	-4.62	3.85	<0.0001
TS5, global and tornado correction	8.58	3.84	-4.75	3.64	<0.0001
TS last, global correction	8.58	3.55	-5.03	4.07	<0.0001
TS last, global and tornado correction	8.58	3.41	-5.17	4.05	<0.0001

^a Paired t test.

^b Behavior scores were summed within a dog.

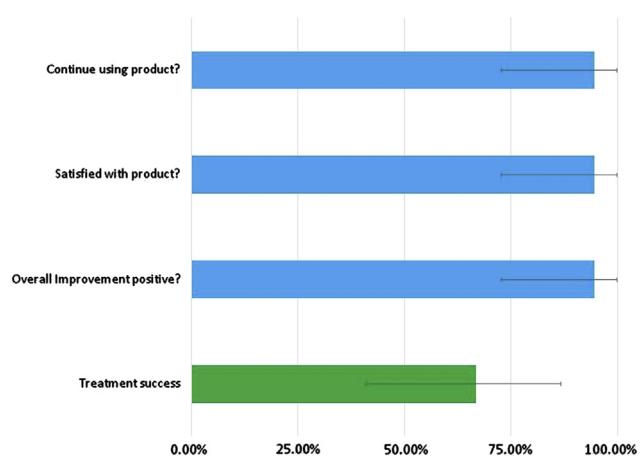


Figure 3. Owner satisfaction and treatment success data.

Table 9

Summary of the assessment of treatment success and owner satisfaction

Item	Percent success	95% Confidence interval
Treatment success ^a	66.67% (12/18)	40.99, 86.66
Owner satisfaction data		
Overall improvement positive?	94.44% (17/18)	72.71, 99.86
Satisfied with product?	94.44% (17/18)	72.71, 99.86
Continue using product?	94.44% (17/18)	72.71, 99.86

^a Success defined by the investigators as an improvement in the behavior score after the 5th storm compared with baseline of at least 1 in 50% of the behaviors identified, with no behavior getting worse.

(Crowell-Davis et al., 2003; Cracknell and Mills, 2008; Gruen and Sherman, 2008; Herron et al., 2008; Ibanez and Anzola, 2009; Ogata and Dodman, 2011). One study has shown no statistically significant difference between dogs whose owners interacted with them during a storm and those that did not (Cottam et al., 2013).

There was 1 possible adverse event during the trial in which 1 subject demonstrated increased anxiety (trembling and refusal to come inside the house) during the first thunderstorm experienced after the first dose of the test article had been administered. The owner was instructed to immediately stop administration and opted to not continue in the trial. It is difficult to say if the test article was the root cause or if the increased anxiety was merely a progression of the phobia itself because of sensitization (Sherman and Mills, 2008). It is feasible that the L-theanine increased sound sensitivity as has been demonstrated in other clinical trials on pharmaceuticals (Ogata and Dodman, 2011). It is interesting to note that this owner later sought consultation services with the primary investigator for a new fear-based behavior unrelated to storm sensitivity.

This study used a small sample of patients. Caution must be exercised when generalizing these results, and further research with a larger subject population and a placebo control is indicated to validate the efficacy shown.

Psychotropic medications including SSRIs (Landsberg et al., 2008; Ibanez and Anzola, 2009), serotonin 2A antagonist/reuptake inhibitors (Gruen and Sherman, 2008), TCAs (Crowell-Davis et al., 2003), alpha-2 agonists (Ogata and Dodman, 2011), and benzodiazepines (Crowell-Davis et al., 2003; Herron et al., 2008; Ibanez and Anzola, 2009) have been studied as treatments for noise phobias and other situational anxieties in dogs. However, daily psychotropic medications including SSRIs and TCAs may have possible obstacles to success including a delayed onset of therapeutic effect of up to 4 weeks (Crowell-Davis and Murray, 2006) and the potential need for an additional situational medication (Crowell-Davis et al., 2003; Gruen and Sherman, 2008; Ibanez and Anzola, 2009). Despite evidence of efficacy in the cited trials, some veterinarians and their clients may be reluctant to use psychotropic medications, limiting potential treatment options and compromising the welfare of those patients suffering from storm sensitivities. Utilization of a nutraceutical product may aid in amelioration of these symptoms and/or allow the owner to understand that additional interventions might be necessary for the animal's well-being.

Conclusion

Noise phobias can affect the welfare of the dog and damage the human-animal bond because of the cost, both emotional and financial (Sherman and Mills, 2008). The present study suggests that the use of L-theanine is an effective treatment for storm sensitivity in dogs. The use of L-theanine decreases the severity of the dog's global anxiety during storms, reduces the time it takes for the dog to return to baseline normal behavior after the storm ends,

and diminishes the most commonly reported manifestations of hiding, following people, pacing, panting, and trembling. Although the study population is small, these results validate anecdotal clinical usage of L-theanine to alleviate anxiety in thunderstorm-sensitive and thunderstorm-phobic dogs. This study mirrors how the veterinary practitioner might use L-theanine as a first-line treatment when presented with a thunderstorm-sensitive patient. The present study gives clinicians an alternative therapeutic option for dogs with storm sensitivities that is safe, effective, easy to administer, and results in overwhelming owner satisfaction.

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Conflict of interest

Dr. Heidi Lobprise, DAVDC, was employed by Virbac Animal Health at the time the study was designed and conducted.

Statements

The idea for the article was conceived by Dr. Debra Horwitz. The experiments were designed by all 3 authors in collaboration. The experiments were performed by Dr. Amy Pike. The data were analyzed by a paid biostatistician (paid for with funding from Virbac Animal Health but who was not an employee of Virbac Animal Health). The article was written by Dr. Amy Pike with editing, additions, and revisions done by the additional authors.

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