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## Research

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

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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 Houpt, 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 Houpt, 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

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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

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