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# Effects of trazodone on behavioral and physiological signs of stress in dogs during veterinary visits: a randomized double-blind placebo-controlled crossover clinical trial

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**OBJECTIVE**
To determine whether a single dose of trazodone administered to dogs before a veterinary visit reduced their behavioral and physiologic signs of stress and owners' stress during veterinary visits.

**SAMPLE**
20 dogs and their owners.

**PROCEDURES**
In this randomized double-blinded placebo-controlled crossover clinical trial, dogs with a history of anxiety during veterinary visits were scheduled for 2 veterinary visits 1 week apart and randomly assigned to receive a single oral dose of either trazodone (9 to 12 mg/kg) or a placebo 90 minutes before transport to the veterinary clinic for alternate visits between September 21 and November 3, 2019. For each visit, we collected and assessed owner-completed surveys of dog stress score (DSS) and owner stress score; various investigator-reported scores, including from video-recorded behavior analyses; and patient-related physiologic data.

**RESULTS**
Dogs treated with trazodone versus placebo had lower mean DSSs, assessed by owners for physical examination and assessed by video analysis for time spent in the examination room; lower mean SD of normal-to-normal intervals, root mean square of successive heartbeat interval difference, and respiratory rate; and higher mean heart rate. No meaningful differences were observed in other behavioral or physiologic outcomes, including serum cortisol concentrations.

**CLINICAL RELEVANCE**
A single dose of trazodone before transport reduced signs of stress during veterinary visits for dogs in the present study and may be useful as an anti-anxiety medication for similarly affected dogs, potentially resulting in higher-quality clinical examinations and improved patient welfare.

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According to the AVMA, 82.8% of dogs in the US were taken by their owners to veterinarians at least once a year in 2016.[1] During veterinary visits, many dogs show signs of fear, anxiety, or stress.[2,3] Stressors may elicit responses in behavioral, cardiovascular, and endocrine changes.[4,5] Signs of stress include escape and avoidance behavior, elevated heart rate (HR), shivering, and, at the extreme end, voiding of urine or feces. Furthermore, some dogs display aggression due to stress and fear, potentially injuring veterinary staff during restraint and treatment.[6–8] Fear-related aggression during examinations can also result in an incomplete physical examination, which could lead to inaccurate or incomplete diagnoses. Stress displayed by pets and the subsequent difficulty of getting their pets to the veterinary hospital were cited as major reasons that owners did not visit a veterinarian.[9] Measures that reduce the stress of veterinary visits for pets could, therefore, improve the quality of veterinary practice and animal health.

One important way to alleviate stress has been a movement toward pet-friendly veterinary practice, in which veterinarians and their staff care for the mental health, as well as the physical health, of animals. Pet-friendly environments,[10] music,[11,12] lower background noise,[13] low-stress handling,[14] and the use of food[15] have been shown to be effective in reducing stress levels during veterinary visits.

Anti-anxiety medications are also an important adjunct to reduce stress in veterinary patients.[16] Trazodone and gabapentin, both short-acting medications used to lower anxiety, have been found to be

effective in relieving stress in cats visiting a veterinary clinic.[17,18] Additionally, the use of dexmedetomidine oromucosal gel decreased stress-related behaviors during physical examination in dogs.[19]

Trazodone, a serotonin antagonist and reuptake inhibitor, has been shown to be an effective adjunct medication for the treatment of canine anxiety disorders[20] and for reducing stress in hospitalized dogs, including during postsurgical confinement, although some results do not fully support its effectiveness.[21–23] Anecdotal clinical reports have suggested that trazodone may also be effective in alleviating stress during veterinary visits[24]; however, to our knowledge, there are no known peer-reviewed studies on the effectiveness of trazodone for this purpose.

The objective of the study reported here was to determine whether a single dose of trazodone (9 to 12 mg/kg, PO) administered to dogs before a veterinary visit reduced their behavioral and physiologic signs of stress and their owners' stress during veterinary visits. We assessed stress based on behavioral observations by owners and investigators alongside physiologic measurements, specifically respiratory rate (RR), serum cortisol concentration, HR, and HR variability (HRV), including root mean square of successive heartbeat interval differences (rMSSD) and SD of normal-to-normal intervals (SDNN). We hypothesized that dogs receiving trazodone (9 to 12 mg/kg, PO) 90 minutes prior to a car ride to the veterinary clinic would display fewer stress-related behaviors, be more easily handled, and have physiologic measurements indicative of lower stress, compared with those receiving a placebo. The results of the study would contribute to the ability to make evidence-based recommendations of trazodone as a preappointment anti-anxiety medication.

# Materials and Methods

## Study design

This study was designed as a randomized, double-blinded, placebo-controlled crossover clinical trial. The study protocol was approved by the Institutional Animal Care and Use Committee of the University of California-Davis.

A study website was developed to recruit dog owners to participate. One initial and 2 follow-up emails were sent to veterinary students and professionals at the University of California-Davis School of Veterinary Medicine. Enrollment criteria for dogs were as follows: 1) history of displaying signs of stress and anxiety during veterinary examinations; 2) clinically normal dogs, 1 to 10 years of age and weighing 5 to 45 kg; 3) no history of biting people; no history of anxiety, nausea, or vomiting during car rides; and 4) could tolerate wearing a harness, so the dog could wear an HR sensor across their thorax. All owners signed a consent form, and all participants fully completed the trial.

Two structured veterinary visits were conducted at the University of California-Davis Veterinary Medical Teaching Hospital over 2 weekends, 1 week apart, between 9 AM and 4 PM. A simple randomization table was used to assign each dog to the treatment that it would receive prior to each visit. All investigators and dog owners were blinded to the treatment assignments. Each dog was scheduled to come to the veterinary clinic at a set date and time and had no contact with any other dog or human participant at any time during the study. To simulate a typical veterinary waiting room, barking dog sounds were played from a mobile device, and one of the investigators (MRB) walked around the room with stuffed toy dogs every 5 minutes. Processed cheese (Easy Cheese American; Nabisco) and baby food (2nd Foods Beef and Gravy; Gerber Products Co) were given to dogs during the physical examination and blood sample collection. If a dog had been trained to wear a muzzle, it was recommended that a muzzle be brought with the dog so it could be used during these treatments.

Each dog was assigned an oral dose of trazodone (9 to 12 mg/kg) based on a published recommendation.[24] Trazodone capsules were prepared by crushing 50-mg tablets of trazodone (Teva Pharmaceuticals) into powder, which was then transferred into opaque, size 0 gelatin capsules (Capsule Supplies LLC). Placebo capsules were prepared using the same gelatin capsules filled with the same weight of lactose powder (Fisher Scientific). All capsules were stored in sealed containers at room temperature in the pharmacy until the study was completed.

## Structured clinical protocol

On the day of the first clinic visit, owners gave the assigned treatment (trazodone or placebo) to their dog 90 minutes prior to transport to the veterinary clinic. For each visit, the owner and dog were greeted upon arrival at the clinic and then escorted to the veterinary clinic waiting room (5 X 6 m), where an HR sensor (H10; Polar Electro Inc) was attached with an elastic band around the thorax of the dog, at the level of the axilla, so that HRV could be recorded by a mobile phone application (Heart Rate Variability Logger; A.S.M.A.B.V). Because body position has been shown to substantially affect HR, the owners were present while the dogs were maintained in a standing position for 5 minutes and then in a sitting position for 5 minutes to compare the 2 baselines.[25] Next, the owner and dog were escorted to a scale, where the dog was weighed. The owner and dog were then taken into the examination room (3 X 3 m), at which time video recording began. Each owner stayed in the examination room with their dog without the investigators for 5 minutes, during which time the owner filled out the first survey **(Supplementary Appendix S1)**, which focused on dog and owner stress during transport, and was instructed to interact with their dog as they typically would at a veterinary clinic. After 5 minutes, investigators returned to the examination room to perform a standardized physical examination, starting from anterior to posterior, and concluding with taking a rectal temperature using a digital thermometer.

Once the examination was completed, the video recording was stopped, and the investigators walked the dog, without the owner, into the treatment room for blood collection from a saphenous vein. During this time, the owner stayed in the examination room and filled out a second survey **(Supplementary Appendix S2)**, which

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focused on dog and owner stress during the veterinary visit. Once blood collection was completed, the HR sensor was detached, and the dog was walked back to the examination room to be rejoined with the owner. This concluded the structured veterinary visit, and then the owner and their dog exited the building. After the owner and dog left, 1 investigator (SK) completed the survey **(Supplementary Appendix S3)** of investigator-reported behavioral scores. One week later, the owners administered the second treatment (double-blinded crossover treatment with either trazodone or placebo), and the same protocol was repeated.

## Behavioral assessments

**Owner-reported scores**—As mentioned earlier, owners were asked to fill out standardized surveys (Supplementary Appendices S1 and S2) to evaluate their dog's level of stress (dog stress score [DSS]) and their own personal stress (owner stress score [OSS]). In each survey, DSS and OSS were scored from 1 to 5 using a Likert-type scale, with 1 being very low stress and 5 being very high stress. After the veterinary visits, the owners were contacted by one of the investigators (SK) and asked 2 additional questions: 1) On which of the 2 visits to the clinic did you feel that your dog received trazodone? and 2) On which visit did your dog seem less stressed?

**Investigator-reported scores**—As mentioned earlier, the investigator (SK) who examined each dog filled out a standardized survey (Supplementary Appendix S3) immediately after each appointment. The survey consisted of 3 sets of observations to assess the dog's levels of sedation, aggression, and compliance during the veterinary visit.

Sedation was assessed at 3 time points: when the dog was in the waiting room, when the dog entered the examination room, and when the investigator entered the examination room 5 minutes later. The scoring scale, modified from Grint et al,[26] was as follows: 0 = no observable sedation, 1 = tired but standing, 2 = lying but able to rise, 3 = lying but had difficulty rising, and 4 = unable to rise.

Aggression was assessed at 7 time points: when the dog was in the waiting room, when the dog entered the examination room, when the investigator entered the examination room 5 minutes later, during the oral examination, during thoracic auscultation, during abdominal palpation, and while taking the rectal temperature. Aggression was scored as follows: 0 = no aggression, 1 = growl, 2 = snarl (growl showing teeth), 3 = snap (head turn, no serious attempt to bite), and 4 = bite or attempt to bite.

Compliance was assessed at 4 time points during the physical examination: during oral examination, during thoracic auscultation, during abdominal palpation, and approximately 5 seconds after inserting the thermometer into the dog's rectum. Compliance was scored as follows: 0 = no resistance to restraint, 1 = minimally resistant to restraint, 2 = struggling and difficult to restrain, 3 = extreme struggling, and 4 = extreme struggling with urination, defecation, or anal gland expression, alone or in combination.

**Video-recorded behavior analysis**—A video camera was set up on a tripod, and it was turned on and off by an investigator (KL). Videos were evaluated by 2 blinded observers who were trained by one of the investigators (SK), were provided written guidelines about the video analysis criteria,[27] and were mock-tested with examples of recorded files. Videos of the dogs were analyzed at 9 time points: the first 15 seconds after both investigators left the examination room; the middle 15 seconds without investigators present; the last 15 seconds before the investigators reentered the examination room; during the examination of the ears, eyes, and mouth; during thoracic auscultation; during abdominal palpation; and while checking the rectal temperature. The DSS was calculated for each dog at each of the 9 time points **(Figure 1)**. Next, the DSSs were separated into 2 groups, the placebo group and the trazodone group. Then, the proportion of the 2 groups' DSSs was calculated and graphed for each of the 9 time points. Finally, the mean was calculated for proportion of DSSs of the 2 groups. The dog stress scoring system used **(Supplementary Appendix S4)**

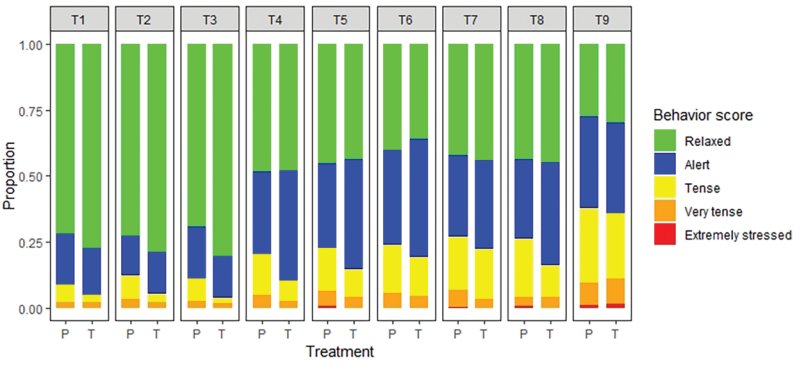



**Figure 1**—Mean video-based DSS (1 = relaxed [green], 2 = alert [blue], 3 = tense [yellow], 4 = very tense [orange], 5 = extremely stressed [red]), as determined by 2 independent observers during video analysis of the dogs described in Figure 1 when in the examination room before (T1 through T3) and during (T4 through T9) physical examinations, expressed as a proportion of 1 for comparison across time points. The mean video-based DSS was significantly ($P < 0.05$) lower for the time points before (T1 through T3) versus during (T4 through T9) the physical examination and higher for the time point during the rectal temperature check (T9) versus time points for other examination procedures (T4 through T8). At all time points, dogs that received trazodone had significantly ($P < 0.001$) lower behavior scores than dogs that received placebo. P = Placebo. T = Trazodone. T1 = First 15 seconds after both investigators left the examination room. T2 = Middle 15 seconds without investigators present. T3 = Last 15 seconds before the investigators reentered the examination room. T4 = Time during the ear examination. T5 = Time during the eye examination. T6 = Time during the oral examination. T7 = Time during thoracic auscultation. T8 = Time during abdominal palpation. T9 = Time during rectal temperature measurement.

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was modified from a stress scoring system utilized in previous research.[27]

## Physiologic measurements

**HR variability**—At each visit, HRV was measured via the same HR monitor and recorded by an app, as mentioned earlier. HRV measures fluctuation in the time interval between adjacent heartbeats (interbeat interval) and is an index of neurocardiac function, which is generated by heart-brain interactions and dynamic nonlinear autonomic nervous system processes.[28] HRV consists of 2 time-dependent measurements: 1) rMSSD, an index of the parasympathetic nervous system, and 2) SDNN, an index of the autonomic nervous system.[29,30] These 2 measurements were calculated by the app and analyzed as indicators of the emotional status of the dogs.[29,30] Dogs' HRs and RRs were also measured and recorded by the HRV sensor and app.

**Serum cortisol**—Blood samples (3 mL) were collected from the saphenous vein. The blood was placed into evacuated glass tubes containing no anticoagulant, clot activators, or other additives and allowed to clot. Serum was separated after 30 minutes and then submitted to the University of California-Davis School of Veterinary Medicine Clinical Pathology Laboratory. Serum cortisol concentration was measured using an autoanalyzer (Immulite 2000; Siemens Healthcare GmbH) and expressed in micrograms per deciliter.

## Statistical analysis

Descriptive statistics were reported as the mean ± SD. Mixed-factor ANOVA with repeated measures was used to evaluate the association of trazodone administration with components of the HRV and behavioral scores from the video-recording analysis. The mixed-factor ANOVA additionally involved the 4 time points of the trial as a fixed effect factor to adjust confounding by observations in 4 different conditions (waiting room, resting in the examination room, physical examination, and blood collection). The individual variability was involved as a random-effect factor in the mixed-effect ANOVA considering the autocorrelation by successive observation of an individual. Pairwise Wilcoxon rank sum tests were used to evaluate the association of trazodone administration with serum cortisol concentration and owner- and investigator-reported scores. Interobserver agreement for the video-recorded behavior analysis was assessed by Cohen κ analysis. Agreement in results was interpreted as follows: slight (κ, 0 to 0.20), fair (κ, 0.21 to 0.40), moderate (κ, 0.41 to 0.60), good (κ, 0.61 to 0.80), or excellent (κ, 0.81 to 1.0). All tests were 2 tailed, and significance was set at $P < 0.05$. All data management, statistical analyses, and visualization were performed with available software (R studio version 3.6.1; R Core Team).

# Results

## Study population

Forty dogs were initially screened for the study. Of these, 18 dogs were excluded because they did not meet the inclusion criteria, and 22 dogs were enrolled. Two enrolled dogs were subsequently excluded from final data analysis: 1 dog attempted to bite the investigators during blood collection and was excluded because of safety concerns, and 1 dog was excluded because 2 different owners attended the 2 veterinary visits. Of the 20 dogs included, 10 were castrated males and 10 were spayed females. The mean age of the dogs was 4.98 ± 2.05 years, and the mean body weight was 18.17 ± 10.32 kg. Two dogs were receiving fluoxetine (1.3 to 1.5 mg/kg, q 24 h) prescribed by their veterinarians for anxiety-related disorders. Muzzles were not required, but 2 dogs had had prior basket muzzle training for veterinary visits and wore them, seemingly comfortably, during physical examination and blood sample collection. No other dogs had muzzle training, nor did other owners ask for a muzzle.

## Behavior assessment

**Owner-reported scores**—Mean DSS, as assessed by the owner during their dog's physical examination, was significantly ($P = 0.005$) lower for dogs when they received trazodone (3.5 ± 1.0), compared with placebo (4.2 ± 0.8; **Figure 2**); no significant difference was identified during other time

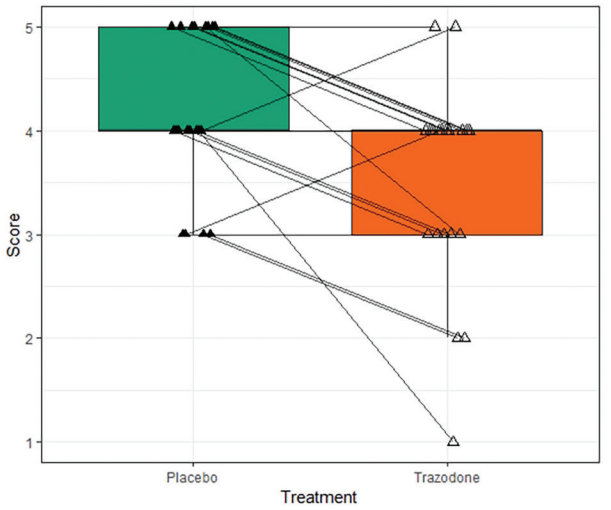



**Figure 2**—Box-and-whisker plots of mean dog stress scores (DSSs) during physical examination as assessed by owners for their dogs (n = 20) in a randomized double-blinded placebo-controlled crossover clinical trial during which dogs with a history of anxiety during veterinary visits were scheduled for 2 veterinary visits 1 week apart and randomly assigned to receive a single oral dose of either trazodone (9 to 12 mg/kg) or a placebo at alternate visits between September 21 and November 3, 2019. Behavior scores were recorded using a Likert-type scale from 1 to 5, with 1 being very low stress and 5 being very high stress. For each plot, the box represents the interquartile range (IQR; trazodone [orange] vs placebo [green]), the whiskers represent 1.5 times the IQR of the first and third quartiles, the bold horizontal line represents the median, and each triangle represents the mean DSS for a dog treated with either a placebo (solid triangles) or trazodone (outlined triangles); the lines connecting triangles across plots indicate results in each treatment for an individual dog.

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points. There was no significant ($P$ = 0.158) difference in OSS between treatment groups. In interviews after the veterinary visit, 90% (18/20) of owners correctly identified on which day the treatment was trazodone and thought their dog was less stressed on that day, compared with the day their dog received the placebo.

**Investigator-reported scores**—There was no significant difference between sedation, aggression, and compliance scores across all the time points for dogs receiving trazodone versus the placebo. A rectal temperature could not be obtained during the visit for 1 dog that had received the placebo.

**Video-recorded behavior analysis**—Based on video analyses across 9 time points while dogs were in the examination room, the mean DSS was significantly ($P$ < 0.001) lower for dogs that received trazodone (1.64 ± 0.83) versus the placebo (1.75 ± 0.91) before the visit (Figure 1). Mean video-based DSSs for all dogs were significantly ($P$ < 0.05) lower for the time points before versus during the physical examination and higher for the time point during rectal temperature check versus time points during other examination procedures. The video-based DSSs of 2 observers showed fair agreement (Cohen κ = 0.325 to 0.368).

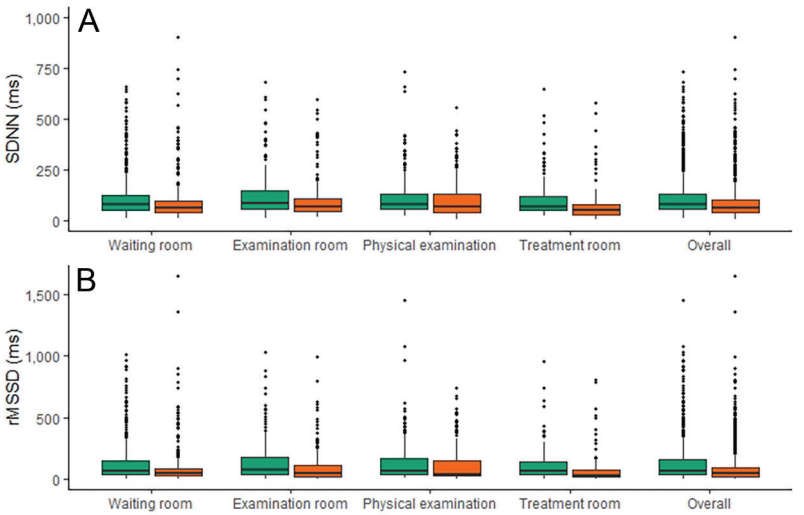



**Figure 3**—Box-and-whisker plots of the SD of normal-to-normal intervals (SDNN; A) and root mean square of successive heartbeat interval differences (rMSSD; B) for the dogs described in Figure 1, grouped by treatment (trazodone [orange] vs placebo [green]), with results considered overall and when grouped on the basis of whether dogs were in the waiting room, resting in the examination room, undergoing physical examination, or in the treatment room undergoing blood collection. For each plot, the box represents the IQR, the central horizontal line in the box represents the median, the represent 1.5 times the IQR of the first and third quartiles, and black dots represent outlier values.

## Physiologic measurements

**HR variability**—The SDNN and rMSSD (components of HRV) and RR were significantly ($P$ = 0.008, $P$ = 0.01, and $P$ < 0.001, respectively) lower and HR was significantly ($P$ < 0.001) higher for dogs that received trazodone, compared with those that received the placebo. These differences remained significant ($P$ < 0.001) across time points when dogs were in the waiting room, resting in the examination room, undergoing physical examination, and undergoing blood collection **(Figures 3 and 4)**.

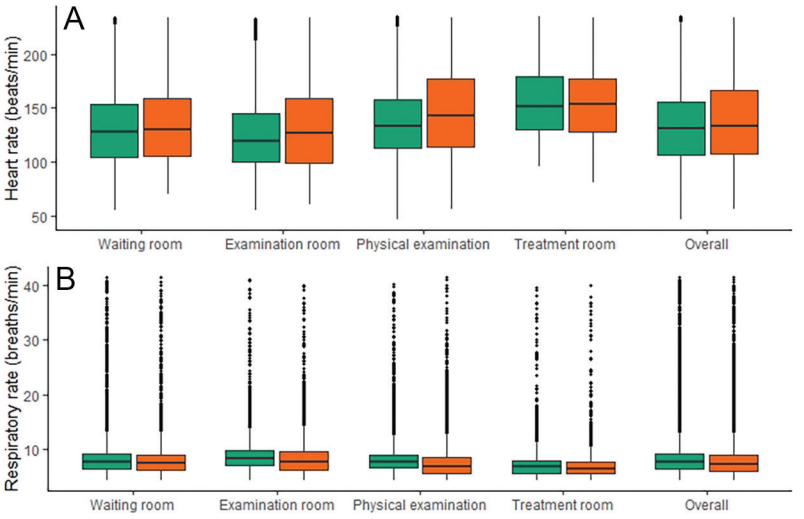



**Figure 4**—Box-and-whisker plots for heart rate (A) and respiratory rate (B) for the dogs described in Figure 1 grouped by treatment (trazodone [orange] vs placebo [green]), with results considered overall and when grouped on the basis of whether dogs were in the waiting room, resting in the examination room, undergoing physical examination, or in the treatment room undergoing blood collection. ***See*** Figure 3 for the key.

**Serum cortisol**—There was no significant ($P$ = 0.896) difference in serum cortisol concentration in dogs that received trazodone (3.56 ± 2.54 µg/dL), compared with placebo (3.40 ± 2.11 µg/dL).

## Adverse effects

Diarrhea was reported for 1 dog approximately 4 hours after administration of trazodone and resolved without treatment. Diarrhea was not reported in the same dog after receiving the placebo.

# Discussion

In the present study, based on owner assessments, video observation analysis, and components of HRV, we found that oral administration of trazo-

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done (9 to 12 mg/kg) 90 minutes prior to transport to a veterinary clinic led to a significant reduction in stress-related behaviors and physiology.

The use of a structured veterinary visit protocol was a strength of the present study that enabled us to tightly control variables in a clinically relevant environment. Within this framework, we found that stress was significantly lower while in the examination room and during physical examination in dogs that received trazodone. More relaxed behavior during physical examination could improve the quality of diagnosis and potentially lead to fewer injuries to veterinary staff.

The trazodone dosage (9 to 12 mg/kg, PO) used in the present study was based on published recommendations,[24] but was higher than that used as an adjunct medication for canine anxiety treatment, stress management during hospitalization, and postsurgical confinement.[20–23] This higher dosage appeared to be well tolerated by most dogs in our study, including the 2 dogs receiving daily fluoxetine. Combining serotonin-enhancing medications can increase the risk of a fatal adverse effect, serotonin syndrome. However, in our study and previous studies,[20,22] no dogs had clinical signs consistent with serotonin syndrome, such as hyperthermia, tremors, or seizures.

We evaluated OSS because a previous study[9] showed that owners delayed bringing their pets to hospitals because it is a stressful experience for both themselves and their pets. In the present study, the OSS did not differ significantly on the basis of treatment (trazodone vs placebo); however, a large percentage (90% [18/20]) of owners reported that they perceived their dogs were less stressed after receiving trazodone, compared with the placebo. If owners perceive that their pets are less stressed, they may be more likely to bring their dogs to a veterinarian for medical care. In addition, because sedation is the most concerning and undesirable effect of trazodone,[31] the lack of observable signs of sedation could provide additional reassurance to owners, who then may more readily accept using trazodone as an as-needed anti-anxiety medication for their dogs.

Investigator-assessed aggression scores did not differ significantly on the basis of treatment, and this finding may have been due to the fact that an inclusion criterion for the study was that dogs had to have no history of biting. All aggression scores were low. One dog attempted to bite the investigators; however, the biting attempts occurred during both placebo and trazodone visits. This could have explained why no differences were seen statistically in the aggression scores. It could have also explained why the aggression scores were low for both trazodone and placebo groups. However, testing for effects of trazodone for aggression may be a challenging study to pursue due to the potential safety concerns that working with aggressive dogs may pose. As such, these are some considerations that future studies should consider.

Investigator-assessed compliance scores did not differ significantly between the treatment groups in our study. One explanation for this result may have been that investigators were highly aware and sensitive to early signs of stress. As such, the handling may have stopped before the dog escalated to increased anxiety and fear, which could have explained the nonsignificant differences in compliance scores. We can presume that dogs that were trained with desensitization and counterconditioning to wear a muzzle would be easier to handle than dogs not trained in this way. We should note that there were differences between the investigators' and owners' scores. Both investigators have specific training and experience in identifying subtle signs of anxiety, stress, and aggression, whereas owners may not be so aware of the subtle signs.

In previous studies, lower rMSSD was considered an indicator of a negative emotional state,[29,30] and only SDNN was lower in a positive situation.[30] In our study, both SDNN and rMSSD were significantly lower when dogs received trazodone. It was not clear why both SDNN and rMSSD were lower for the trazodone-treated dogs in our study; however, it could have been because a veterinary visit is a mixture of multiple emotional experiences. HRs for dogs in the trazodone group were significantly higher than in the placebo group, consistent with findings in a previous study[32] of dogs, where increased HR persisted for 60 minutes after oral administration of trazodone. The administration of high-value treats during the veterinary visit was a confounding factor that could have affected changes in HR. A decrease in appetite is a sign of anxiety and fear, whereas an increase in appetite can be a sign of an animal being less anxious. However, a less anxious dog with an appetite stimulated by a high-value treat may become excited about receiving the treat, which can cause an elevation in HR. Future studies that limit extraneous excitatory triggers, such as treats, when evaluating the effect of anti-anxiety medication on HR are warranted.

Studies[33–35] show high concentrations of serum cortisol to be an indicator of acute psychological stress, with concentrations peaking approximately 15 minutes after a stressful event. We chose to measure serum cortisol concentration because venous blood sampling is a potential stress-inducing event during routine veterinary visits. However, at the time of blood collection, the dogs already had been through multiple stress-inducing situations, including a 10- to 20-minute car ride, a 10-minute wait in the waiting room, a 5-minute wait in the examination room, and a 5-minute physical examination, limiting the ability of serum cortisol to identify stress during a single event. We also did not measure baseline cortisol concentration in the dogs, which would have provided a more meaningful comparison of pre- and postvisit stress. It is challenging to collect previsit blood samples; however, measuring salivary cortisol may be a feasible way to do so in the future. Serum and salivary cortisol concentrations are highly correlated in dogs, and saliva can be collected noninvasively.[36] It would be informative to compare salivary cortisol concentration before, during, and after a veterinary visit.

We purposefully timed administration of trazodone to be 90 minutes prior to the car ride based

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on previous studies[20,22,23] in which owners observed a calming effect in their dogs within 0.5 to 2 hours after administration of trazodone. The median duration of action of trazodone is ≥ 4 hours, likely accounting for most owners reporting that their dogs were more relaxed at home after the veterinary visit when they received trazodone. Measuring behavioral and physiologic responses to stress in dogs after they return from a veterinary visit could provide insight into whether trazodone would be beneficial for recovery after stressful experiences.

Previous studies[37–39] show comorbidity for dogs with fear, anxiety, or both and overall aggression, including aggression toward veterinarians. Dogs with fear or anxiety issues at a veterinary clinic may be more likely to have other problem behaviors. For dogs with comorbid problem behaviors, behavioral therapy other than just a premedication for veterinary visits would be required. There was little aggression displayed by dogs in our study, perhaps due to our selection criterion that dogs had no history of biting veterinary professionals or other people.

Findings in our study provided important groundwork for the evidence-based use of trazodone for alleviating canine anxiety associated with visits to the veterinarian; however, further studies are warranted to evaluate the effect of multiple doses, different dosages, and the timing of doses. Such studies could provide better guidance for the ideal dosing schedule for the most positive effect.

In summary, trazodone was an effective, rapid-onset medication for decreasing stress-related behaviors and physiologic indications of stress during veterinary visits, especially during physical examination, for dogs of the present study. We believe that our results provided sufficient evidence for practitioners to use trazodone as an anti-anxiety medication prior to veterinary visits to improve dogs' physical and emotional health. With a decrease in dogs' stress during a veterinary visit, one can expect higher-quality clinical examinations while improving the welfare of the patient.

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The authors declare that there were no conflicts of interest.

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## Supplementary Materials

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