Effects of trazodone on behavioral signs of stress in hospitalized dogs

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OBJECTIVE
To determine the effects of trazodone treatment on behavioral signs of stress in hospitalized dogs.

DESIGN
Prospective observational study.

ANIMALS
120 client-owned dogs.

PROCEDURES
Hospitalized dogs administered trazodone (n = 60) were observed for stress-related signs or behaviors ≤ 45 minutes after the drug was administered (time 1) and approximately 90 minutes later (time 2). Dogs that did not receive trazodone (n = 60) were selected to serve as controls for environmental stimuli that could affect behavior and were observed at the same times. Signs or behaviors (scored as present or absent) were assessed individually and grouped into behavioral summation categories (frenetic [lip licking, pacing, panting, spinning, trembling, wet dog shake, whining, and yawning], freeze [averting gaze, pinning back ears, and whale eye sign], or fractious [growling, lunging, showing teeth, and snapping], with lifting of a forelimb and pupil dilation included in all categories). Results were compared between groups and within groups over time. Logistic regression was performed to assess associations between reduction in stress-related signs or behaviors and trazodone administration while controlling for environmental influences.

RESULTS
Lip licking, panting, and whining were reduced (defined as present at time 1 and absent at time 2) in trazodone-treated but not environmentally matched dogs. The median number of stress-related behaviors and of frenetic and freeze behaviors was significantly lower at time 2, compared with time 1, in trazodone-treated dogs. Odds of reduced panting and reduced frenetic behaviors at time 2 for trazodone-treated dogs were > 2 times those for environmentally matched dogs.

CONCLUSIONS AND CLINICAL RELEVANCE
Results indicated that trazodone administration reduced stress-related signs and behaviors in hospitalized dogs and may thereby improve patient welfare. (*J Am Vet Med Assoc* 2016;249:1281–1291)

The health implications related to stress during hospitalization have become increasingly recognized in human and veterinary medicine, especially with respect to susceptibility to infection,[1–3] delayed wound healing,[4,5] and gastrointestinal distress.[6,7] Stress associated with hospitalization also has implications for the welfare of patients.[8] The effects of stress have been investigated in numerous canine populations, including research colony,[9] shelter-housed,[10–13] working,[14] and hospitalized[15–21] dogs. Hospitalized dogs specifically have signs of acute and chronic psychogenic stress resulting from invasive procedures, novel environments, confinement, and separation from familiar individuals.[15–21] Dogs hospitalized for surgery have behavioral and physiologic signs of preoperative,[17] perioperative,[18,22] and postoperative[18] stress. Results of 1 study[23] indicated that 106 of 135 (79%) dogs seen in a veterinary clinic had signs of fear, which is a behavioral indicator of stress.[24]

Methods of evaluating stress in hospitalized canine patients include physiologic measurements and behavioral observations. The physiologic variables investigated often include hypothalamic-pituitary-adrenal axis hormones (usually cortisol),[24–28] salivary immunoglobulin A,[29,30] the neutrophil-to-lymphocyte ratio,[26] and heart rate or heart-rate variability.[17,25,31] Physiologic data collection can require invasive methods, and the use of such methods can inadvertently alter the results.[16] Behavioral observation methods vary widely but generally rely on assessment of features or behaviors typically associated with anxiety, including posture and locomotive

ABBREVIATIONS
CI Confidence interval

activity, changes in locomotive activity, vocalization, panting, facial expressions, manipulation of the environment, attempts to flee, oral behaviors (snout licking, lip licking, and lip smacking), and shaking.[15,17–19,24,25,27,32,33] Expression of behavioral signs can differ among dogs in similar circumstances[15] and can follow distinct patterns, depending on the type of stimuli to which the animals have been exposed.[16,34]

Historically, acepromazine maleate, a phenothiazine derivative classified as a tranquilizer that has sedative properties but negligible anxiolytic benefit to animals,[22,35–37] has been used to decrease the clinical manifestations of stress in hospitalized dogs such as vocalization and locomotor activity. Acepromazine can cause a paradoxical excitation, disinhibition of aggression, and a range of physiologic effects[35,36] that could be undesirable in hospitalized patients. Additionally, although it might mitigate the clinical manifestations of stress by sedating patients, acepromazine treatment is not expected to decrease the detrimental health or welfare implications resulting from stress. There is a need for a well-tolerated, orally administered, fast-acting agent to provide anxiolytic benefits to mitigate stress caused by hospitalization, rather than only addressing the clinical manifestations of that stress.

Trazodone hydrochloride has been used in human patients as an antidepressant[38,39] and anxiolytic[40,41] for many years. A member of the phenylperazine class of drugs, trazodone is classified as a serotonin antagonist and reuptake inhibitor owing to its primary pharmacological mechanism as an antagonist at serotonin 2A receptors and its secondary mechanism as a serotonin reuptake inhibitor.[42] In dogs, the drug has been used to treat behavioral disorders[43] and to facilitate postsurgical confinement and calming.[44] It is also recommended to promote low-stress handling during veterinary visits for dogs that have signs of anxiety.[45] In 1 study,[44] the median latency to trazodone effect in 36 dogs (as reported by owners in weekly surveys) was 31 to 45 minutes, with > 90% of owners indicating their dogs had a behavioral response ≤ 90 minutes after trazodone administration. Published dosages of orally administered trazodone range from 1.7 to 19.5 mg/kg/d (0.77 to 8.86 mg/lb/d; combined daily [q 8 to 24 h] and as-needed administration)[43] or from 2 to 10 mg/kg (0.91 to 4.55 mg/lb) up to every 8 hours on an as-needed basis[46] for treatment of dogs with signs of anxiety; from 7 to 10 mg/kg (3.18 to 4.55 mg/lb), every 8 to 12 hours for postsurgical confinement[44]; and from 4 to 12 mg/kg (1.81 to 5.45 mg/lb), 90 minutes prior to a veterinary hospital visit, to reduce stress associated with handling and examination.[45] Trazodone administration should not exceed 300 mg/dose or 600 mg/24 h.[43]

A pharmacokinetics study[47] of a single dose of trazodone (8 mg/kg [3.64 mg/lb]) given to adult Beagles revealed that the orally administered drug induced mild sedation with no adverse effects. When used clinically alone or in combination with other medications, including tramadol, NSAIDs, antimicrobials, and various behavior-modifying drugs, trazodone was also well-tolerated by dogs, with few observed adverse effects, which typically included gastrointestinal distress, behavioral changes, or sedation.[43,44]

To the authors' knowledge, no studies to date have specifically examined the use of trazodone to mitigate signs of hospitalization-induced stress in dogs. The purpose of the study reported here was to determine the effects of trazodone administration on expression of behavioral indicators of stress in a population of hospitalized dogs. We hypothesized that patients receiving trazodone would less frequently have behavioral indicators of stress after treatment, compared with findings for the same dogs shortly after drug administration, and that no behavioral changes would be noted in environmentally matched hospitalized dogs (ie, those exposed to similar environmental conditions) that did not receive this medication.

Materials and Methods

Animals and housing

The study was conducted at The Ohio State University Veterinary Medical Center from June 22 to October 8, 2015. Dogs admitted to the hospital were enrolled in the study if the clinician from the admitting service prescribed trazodone hydrochloride[a] at any time during hospitalization (treatment group dogs). Additionally, dogs not administered trazodone were enrolled to control for environmental variables that could be associated with stress during the observation period, such as building construction, fire drills, and inclement weather (environmentally matched group dogs). One environmentally matched dog was selected for each treatment dog, and behavioral observations were performed for each pair of dogs, one immediately after the other, in a given observation period. Environmentally matched dogs were selected on the basis of proximity and similarity in housing environment to the treatment dogs. Dogs were excluded from both the treatment and environmentally matched groups if they had been administered oral or injectable mentation-altering medications ≤ 2 hours prior to observation, except as described in the experimental procedures section.

Dogs were housed in a stainless steel cage in 1 of 4 identical 24-cage wards or in kennels in a single ward divided into 4 discrete sections. Each kennel had siding along its entire length, comprising a concrete barrier 1.22 m (4 feet) high, topped by wire fencing 1.83 m (6 feet) high, for a total height of 3.05 m (10 feet). Each kennel had doors made of the same wire fencing at the front and back. The back of the kennels faced a concrete wall and the front faced an aisle. Housing was determined according to the size of patients (with larger dogs placed in kennels when possible) and the admitting hospital service. The study was approved by The Ohio State University Veterinary Medical Center Clinical Research Advisory Committee and exempted from the

need for approval by The Ohio State University Institutional Animal Care and Use Committee.

Trazodone administration

Trazodone was administered as a standard-of-care treatment for dogs at The Ohio State University Veterinary Medical Center that had signs of fear, anxiety, or aggression on initial evaluation or at any time during subsequent hospitalization, unless contraindicated for the patient. Trazodone was administered by a veterinary student, a veterinary assistant, or a technician. The trazodone was hidden inside a soft treat designed for the purpose[b] or in a meatball formed of palatable canned food, which was hand fed to the dog or placed on the floor of its cage or kennel. Each dog was observed to ensure the drug was consumed. For patients with dietary sensitivities or restrictions, a canned food or soft treat appropriate for that patient (provided by the owner in some cases) was used. By hospital policy, the treatment was not routinely administered to patients for which food was being withheld (eg, in the hours prior to surgery) or that were not fed orally.

In accordance with previously published dosages, trazodone administration was started at 4 mg/kg, every 12 hours, with the dose or frequency increased to 10 to 12 mg/kg[45,46] or to every 8 hours[43] when needed for desired calming and anxiolytic effects, and the amount given did not exceed 300 mg/dose or 600 mg/24 h.[43,45] Trazodone was started at a dosage of 3.5 mg/kg (1.59 mg/lb), every 12 hours, in some dogs that had undergone surgery and were concurrently administered tramadol hydrochloride,[44] at the discretion of the administering clinician. Trazodone administration was continued for the duration of the hospital stay as needed, with adjustments made to account for changes in signs of anxiety at the discretion of the attending clinician. Additionally, trazodone was dispensed to clients for administration to dogs to help facilitate postoperative confinement at home when deemed necessary by the clinician responsible for the case.

Experimental procedure

When a clinician in the orthopedic surgery, soft-tissue surgery, emergency and critical care, internal medicine, or neurology service initiated trazodone treatment of a hospitalized dog, the clinician contacted the first author (SGG). Clinicians in these services had been informed of the study through verbal and written communication from the first author, and a flyer containing detailed information regarding the study and contact information had been provided to post in each service's wards. The ward location, name and weight of the patient, and dosage of trazodone administered were recorded. The study did not interfere with the timing or dosages of treatments administered by the admitting service staff. Therefore, it was not possible to observe baseline behavior prior to trazodone administration, and the first author was notified at the time that trazodone was administered to the patient. The hospital treatment sheet was examined, and admitting service staff were questioned to ensure no mentation-altering medications, including sedatives, had been administered ≤ 2 hours before trazodone administration or to ensure the mentation changes from such medications would either already have been in full effect or been fully resolved prior to trazodone administration, before a dog was included in the study. Lights were left on in the wards housing patients to be observed. The first author selected a dog housed ≥ 3 cages or kennels to the right (or to the left if there was no dog to the right) within the same ward to serve as a control for environmental conditions that could influence patient stress. The distance between trazodone-treated and environmentally matched dogs was such that when one dog was being observed, the observer could not be seen by the other dog. If there were no other dogs in the ward, the first dog on the right end of the cages or kennels in the nearest adjacent ward was selected. If no dogs were housed in an adjacent ward, the first dog on the right end of the cages or kennels in the next ward was selected.

Opaque cards were placed over the treatment sheets of each pair of dogs so that all identifying information and the treatment plan were obscured when a trained observer (MRR) entered the ward or wards to perform behavioral observations. After paired dogs had been selected for study inclusion, the observer was contacted immediately and informed of the ward locations of the 2 patients to be assessed. The observer, who remained blinded to identification and study treatment allocation of the dogs, performed 60-second behavioral observations for each of the dogs at 2 time points. Dogs were observed in the same order at both time points. The first observation (time 1) was performed ≤ 45 minutes after trazodone was administered to the dog receiving treatment, and the second observation (time 2) was performed approximately 90 minutes after the first. When a dog was enrolled in the study, admitting service staff were asked to alert the first author to any observed adverse effects attributable to trazodone administration at the time the reaction was detected (at any time during hospitalization). Additionally, each week of the study, admitting service personnel were queried about any adverse effects observed in treatment group dogs that week, in case the clinician had not contacted the first author at the time of an observed adverse reaction.

Behavioral assessment checklist and observer training

A checklist was developed by the first author in conjunction with a board-certified veterinary behaviorist (MEH). The checklist was initially created as a scoring tool to assess 22 stress-related signs or behaviors, including those associated with fear, anxiety, and aggression, over the described 60-second observation period. These included lifting of a forelimb, dilation of pupils, lip licking, pacing, panting, spinning,

trembling, shaking (wet dog shake), whining, yawning, averting gaze, pinning back ears, widening of the eyes (whale eye sign), hiding in the back of the kennel, hunching the hindquarters, flattening the body onto the ground, freezing behavior, tail tucking, growling, lunging, showing teeth, and snapping. The checklist was further refined for ease of use and reliability in a hospital environment through use by veterinary students and staff, such that the final checklist used in the study included 17 stress-related signs or behaviors **(Appendix)**. Behaviors that were excluded from the final list (hiding in the back of the kennel, hunching the hindquarters, flattening the body onto the ground, and freezing behavior) were found to be difficult for several participants to distinguish as indicators of stress, because similar body postures or behaviors resulting from physical limitations or from patient discomfort were often seen. Because physical limitations or discomfort arising from injury, illness, or surgery would be expected in some hospitalized dogs, these behaviors were considered unreliable indicators of stress for the population to be studied.

The first author mentored the observer on the proper identification of each stress-related sign or behavior over a 2-week period prior to the start of the study. Following this training, a preliminary investigation was performed in which all hospitalized dogs housed at the study facility (n = 100) were scored separately and concurrently by the first author and the observer over a 2-week period. This was done to ensure the checklist could be used to identify stress-related signs or behaviors in dogs hospitalized at the facility. Interobserver reliability between the 2 investigators was evaluated. The checklist was also used by the study observer to score video recordings of 20 dogs at 2 time points, 4 weeks apart, for assessment of intraobserver reliability.

Behavioral assessments

For each study assessment, the observer entered the ward and approached the cage or kennel, remaining 0.91 m (3 feet) away, to observe the patient for 30 seconds. The observer then stepped up to the cage or kennel door and observed the patient for an additional 30 seconds. During the 60-second period, the observer recorded the patient's behavior and signs reflecting stress as present or absent by use of the checklist. The observer did not come into physical contact with the dogs or their cages or kennels, did not speak to the dogs, and did not otherwise interact with the dogs at any time during the study.

After observation, the number of observed stress-related signs or behaviors was summed for each dog. The signs or behaviors were also grouped into 3 behavioral summation categories (frenetic, freeze, and fractious), so that each dog had a total stress-related behavior score and a behavioral summation score. The subgroups were named to describe an individual dog's manifestation of stress-related behaviors in a way that was considered intuitive to veterinary professionals other than behavior specialists. The categories were created to capture changes in response to trazodone administration in animals that had expression of only a few of the predetermined signs. This allowed for the identification of changes in signs of stress that might have been missed if only a total score was examined. Additionally, the categories provided a means to assess whether the response to trazodone differed between patients with different types of stress-related behaviors and to potentially identify a subgroup of dogs that would have a greater or lesser benefit from the treatment.

Frenetic behaviors included lip licking, pacing, panting, spinning, trembling, whining, yawning, and wet dog shake. Freeze behaviors included averting gaze, pinning back ears, and whale eye sign. Fractious behaviors included growling, lunging, showing teeth, and snapping. Because pupil dilation is a sensitive indicator of sympathetic arousal or hypothalamic-pituitary-adrenal axis activation for a visually sound patient in a well-lit room,[48] and arousal is involved in any type of stress expression, this sign was included in all 3 categories. Lifting of a forelimb was also included in all 3 categories because it is a compound behavior of an active movement followed by a distinct freeze and can be an overt warning of aggression.[49,50]

Statistical analysis

Inter- and intraobserver agreement for the behavioral assessment checklist in preliminary experiments were assessed by Cohen κ analysis. The results were 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) agreement.[51]

Descriptive statistics were computed for all demographic variables stratified by group (trazodone treatment vs environmentally matched). Distribution of the data was visually assessed for normality by examination of histograms. For statistical analyses, breed type was defined as purebred or mixed breed. Total stress-related behavior scores (calculated as the total number of signs or behaviors observed) ranged from 0 to 17. The behavioral summation scores ranged from 0 to 10 for frenetic behaviors, 0 to 5 for freeze behaviors, and 0 to 6 for fractious behaviors. Demographic data were compared between the treatment and environmentally matched groups with independent *t* tests (normally distributed continuous variables), Wilcoxon rank sum tests (nonnormally distributed continuous variables) and Pearson χ^2 or Fisher exact tests (categorical variables). Given the paired nature of observations over time by dog, the exact 2-sided McNemar test and Wilcoxon signed rank test were used to independently examine changes (from present to absent or vice versa) in each observed sign or behavior and changes in summation behavior scores, respectively, for the 2 groups.

Results were further evaluated to determine whether dogs had a reduction in stress-related signs

or behaviors over time (scored as yes when a sign or behavior was present at time 1 and absent at time 2, or when a behavioral summation score was higher at time 1 than at time 2), and exact matched (by treatment-environmentally matched pair) logistic regression was used to assess associations between reduction in stress-related signs or behaviors and trazodone administration for individual and summation variables while controlling for environmental influences. The ORs and 95% CIs were calculated for each outcome. Values of $P \leq 0.05$ were considered significant in all analyses. Data were analyzed with statistical software.[c]

Results

In the preliminary investigation performed prior to assessment of study dogs, evaluation of interobserver reliability revealed excellent agreement ($\kappa = 1$) between the 2 investigators for findings on the behavioral assessment checklist. Intraobserver reliability when the checklist was used to score video recordings was good ($\kappa = 0.80$).

A total of 120 dogs were enrolled in the study (60 each in the trazodone treatment and environmentally matched groups). One dog in the treatment group was removed because the first observation was performed

Table 1—Demographic and initial behavioral assessment data for dogs treated with trazodone (n = 59) and for environmentally matched dogs that did not receive trazodone (58) in a study to evaluate effects of the drug on behavioral signs of stress in dogs admitted to a veterinary teaching hospital from June 22 to October 8, 2015.

Variable	Treatment group	Environmentally matched group	*P* value
Age (y)	6.2 ± 3.9	5.4 ± 3.6	0.19†
Weight (kg)	28.5 ± 14.0	27.7 ±15.4	0.79†
Breed type			0.31‡
Purebred	39 (66)	44 (76)	
Mixed breed	20 (34)	14 (24)	
Sex and reproductive status			0.61‖
Sexually intact female	5 (8)	4 (7)	
Spayed female	27 (46)	25 (43)	
Sexually intact male	6 (10)	11 (19)	
Neutered male	21 (36)	18 (31)	
Admitting service			0.18‖
Emergency-intensive care	3 (5)	1 (2)	
Internal medicine	3 (5)	3 (5)	
Neurology	4 (7)	1 (2)	
Orthopedic surgery	31 (53)	26 (45)	
Soft-tissue surgery	18 (31)	23 (40)	
Other	0 (0)	4 (7)	
Receiving mentation-altering medications (other than trazodone)	19 (32)	17 (29)	0.84‡
Surgical status at evaluation*			0.015‡
Observed before surgery	40 (74)	25 (50)	
Observed after surgery	14 (26)	25 (50)	
Interval between observations (min)	96.7 ± 6.3	96.7 ± 4.9	1.00†
Duration of hospitalization at observation (d)	1.5 ± 0.8	2.0 ± 2.0	0.01†
Behavioral scores at time 1 (median [range])			
Total stress-related behavior	5 (0–8)	4 (0–8)	0.001¶
Behavioral summation category			
Frenetic	3 (0–6)	2 (0–6)	< 0.001¶
Freeze	3 (0–5)	2 (0–5)	0.039¶
Fractious	1 (0–2)	1 (0–3)	0.098¶

Data are mean ± SD or number (%) unless otherwise indicated. Dogs that were administered trazodone by admitting service staff were included in the treatment group. When notified that a dog was given trazodone, 1 investigator selected an environmentally matched dog as a control for effects of environmental conditions that could contribute to stress (only). An investigator who was blinded to identification and group assignment of the dogs performed behavioral observations for each pair of dogs by use of a checklist at time 1 (≤ 45 minutes after trazodone administration) and time 2 (approx 90 minutes after time 1). In post hoc analysis, the observed signs or behaviors (lifting of a forelimb, dilation of pupils, lip licking, pacing, panting, spinning, trembling, shaking [wet dog shake], whining, yawning, averting gaze, pinning back ears, widening of eyes [whale eye sign], growling, lunging, showing teeth, and snapping) were counted for each dog to determine a total stress-related behavior score at each time point. Signs or behaviors were then categorized as frenetic (lip licking, pacing, panting, spinning, trembling, wet dog shake, whining, and yawning), freeze (averting gaze, pinning back ears, and whale eye sign), or fractious (growling, lunging, showing teeth, and snapping), with lifting of a forelimb and pupil dilation included in all categories, and the counts in each category were used to assess behavioral summation scores for each dog at each time point. Sixty dogs were initially enrolled in each group; 1 dog in the treatment group and 2 in the environmentally matched group were removed because of study protocol failures. Values of $P \leq 0.05$ were considered significant for all analyses.

*Not all dogs had surgery, thus the total is less than the number of dogs in the group. †Independent-samples *t* test. ‡Pearson χ^2 analysis. ‖Fisher exact test. ¶Wilcoxon rank sum test.

> 45 minutes after trazodone administration. Two dogs from the environmentally matched group were removed when behavioral observations could not be performed at time 2 because they were not present in the ward at that time. For 57 of 60 (95%) pairs of dogs, environmentally matched dogs were housed in housing equivalent to that of trazodone-treated dogs, either the same ward or similar type house (cage vs run) in an environmentally equivalent ward.

The mean ± SD trazodone dose administered to dogs in the treatment group was 4.65 ± 0.97 mg/kg (2.11 ± 0.44 mg/lb) with a range of 2.83 to 6.75 mg/kg (1.29 to 3.07 mg/lb). The mean ± SD interval from trazodone administration to time 1 was 13.4 ± 9.6 minutes (range, 2 to 43 minutes) and that from trazodone administration to time 2 was 110.6 ± 9.8 minutes (range, 94 to 138 minutes).

Demographic data were summarized for the 2 study groups **(Table 1)**. Age, body weight, sex, the proportion of mixed-breed versus purebred dogs, admitting service, interval between time 1 and time 2 behavioral observations, and the proportion of dogs receiving mentation-altering medications other than trazodone were not significantly different between the treatment and environmentally matched groups. There was a significant ($P = 0.015$) difference in surgical status between groups; of 54 surgical patients in the treatment group, 74% had surgery pending and 26% were recovering from surgery, whereas of 50 environmentally matched surgical patients, 50% were in each of these categories. There was also a significant ($P = 0.01$) difference in the mean duration of hospitalization on the day of observation, which was shorter for the treatment group than for the environmentally matched dogs (1.5 ± 0.8 days [range, 1 to 4 days] vs 2.0 ± 2.0 days [range, 1 to 11 days]). At time 1, median total stress-related behavior scores and median frenetic and freeze behavior summation

Table 2—Changes in stress-related signs or behaviors for the same 59 trazodone-treated dogs and 58 environmentally matched dogs as in Table 1.

Sign or behavior	Group	No. (%) of dogs with reduction	No. (%) of dogs with increase	*P* value*
Lifting a forelimb	Treatment	5 (8)	2 (3)	0.45
	Environmentally matched	1 (2)	2 (3)	1.0
Pupil dilation	Treatment	7 (12)	5 (8)	0.77
	Environmentally matched	13 (22)	5 (9)	0.096
Lip licking	Treatment	17 (29)	4 (7)	0.007
	Environmentally matched	11 (19)	8 (14)	0.65
Pacing	Treatment	5 (8)	0 (0)	0.063
	Environmentally matched	3 (5)	0 (0)	0.25
Panting	Treatment	20 (34)	1 (2)	< 0.001
	Environmentally matched	8 (14)	3 (5)	0.23
Spinning	Treatment	0 (0)	0 (0)	1.0
	Environmentally matched	0 (0)	0 (0)	1.0
Trembling	Treatment	5 (8)	6 (10)	1.0
	Environmentally matched	3 (5)	1 (2)	0.63
Wet dog shake	Treatment	0 (0)	0 (0)	1.0
	Environmentally matched	0 (0)	0 (0)	1.0
Whining	Treatment	14 (24)	2 (3)	0.004
	Environmentally matched	8 (14)	5 (9)	0.58
Yawning	Treatment	0 (0)	1 (2)	1.0
	Environmentally matched	2 (3)	3 (5)	1.0
Averting gaze	Treatment	6 (10)	4 (7)	0.75
	Environmentally matched	13 (22)	11 (19)	0.84
Pinning back ears	Treatment	10 (17)	5 (8)	0.30
	Environmentally matched	6 (10)	9 (16)	0.61
Whale eye sign	Treatment	14 (24)	2 (3)	0.004
	Environmentally matched	14 (24)	4 (7)	0.031
Growling	Treatment	0 (0)	1 (2)	1.0
	Environmentally matched	1 (2)	0 (0)	1.0
Lunging	Treatment	0 (0)	0 (0)	1.0
	Environmentally matched	1 (2)	0 (0)	1.0
Showing teeth	Treatment	0 (0)	0 (0)	1.0
	Environmentally matched	0 (0)	0 (0)	1.0
Snapping	Treatment	0 (0)	0 (0)	1.0
	Environmentally matched	0 (0)	0 (0)	1.0

Signs or behaviors present at time 1 and absent at time 2 were counted as reduced, and those absent at time 1 and present at time 2 were counted as increased.

*Exact 2-sided McNemar test. The *P* value is an indicator of the probability that dogs were equally likely to have a reduction in the occurrence of a behavior versus an increase in the occurrence of a behavior. Dogs that did not have changes in the presence or absence of a behavior between time points do not contribute to the statistic and are excluded from the table.

See Table 1 for remainder of key.

scores were significantly ($P < 0.04$ for all comparisons) higher for the treatment group than for the environmentally matched group; however, fractious behavior summation scores did not differ between groups at this evaluation.

Changes in stress-related signs or behaviors

Trazodone treatment resulted in a significant reduction in the observations of several stress-related signs or behaviors (ie, absence of a characteristic at time 2 when it was present at time 1), including lip licking ($P = 0.007$), panting ($P < 0.001$), whining ($P = 0.004$), and whale eye sign ($P = 0.004$; **Table 2**). With the exception of whale eye sign ($P = 0.031$), reductions in stress-related signs or behaviors were not observed after the same interval for environmentally matched dogs. Similarly, median total stress-related behavior scores and median frenetic and freeze behavior summation scores were significantly ($P \leq 0.009$) lower at time 2, compared with time 1, for dogs in the treatment group **(Table 3)**. No significant changes were identified between time points for these summary variables for environmentally matched dogs.

Exact logistic regression performed to assess effects of trazodone while accounting for environmental effects on stress indicated a significant effect of treatment on reduction of some stress behaviors; dogs in the treatment group had greater odds of a reduction in panting (OR, 2.7; 95% CI, 1.0 to 8.3; $P = 0.050$) and reduction in frenetic behaviors (OR, 2.3; 95% CI, 1.0 to 5.8; $P = 0.040$), compared with dogs in the environmentally matched group. No other significant differences were identified between groups in this analysis.

Adverse events

One dog, admitted through the neurology service because of an intervertebral (C3-4) disk extrusion, with normal mentation and no history of aggression, had trazodone administration discontinued because of signs of aggression (growling, lunging, and snapping) 60 minutes after trazodone administration on the day of admission (with growling noted by the observer at time 2). Administration of diazepam (0.5 mg/kg [0.23 mg/lb] IV, q 6 h) had been initiated for this dog on the same day, and the diazepam was discontinued owing to concern over disinhibition of aggression. The dog underwent a hemilaminectomy the following morning and had no signs of aggression that evening; a second dose of trazodone was administered after the patient recovered from surgery. The dog had the same signs of aggression 60 minutes after trazodone administration, and trazodone treatment was discontinued for this dog by the admitting service. No other adverse events were reported.

Concomitant medications

During the study, 32 of 59 (54%) dogs that received trazodone were administered ≥ 1 concomitant medication prescribed by admitting service clinicians. Most of these dogs received NSAIDs (carprofen, deracoxib, tepoxalin, firocoxib, or meloxicam; n = 18) or tramadol (14). Nine dogs were administered gastroprotectants (omeprazole, sucralfate, pantoprazole sodium, or famotidine). Other medications included systemic antimicrobial treatments (metronidazole, cephalexin, amoxicillin-clavulanic acid, enrofloxacin, ampicillin sodium–sulbactam sodium, marbofloxacin, or amikacin sulfate; n = 6), opioids (hydromorphone hydrochloride, butorphanol tartrate, fentanyl citrate, or methadone hydrochloride; 6), a tranquilizer (acepromazine maleate; 5), an antiepileptic with analgesic effects (gabapentin; 4), a corticosteroid (prednisone; 4), antiemetics (ondansetron hydrochloride, maropitant citrate, or metoclopramide hydrochloride; 4), an antihistamine (diphenhydramine hydrochloride; 3), an appetite stimulant (mirtazapine; 1), a laxative (lactulose; 1), and an anthelmintic (fenbendazole; 1). No adverse events attributable to concomitant medication administration were reported.

Table 3—Results of analysis for differences in total stress-related behavior and behavioral summation category scores for the same 59 trazodone-treated dogs and 58 environmentally matched dogs as in Table 1.

Variable	Group	Score		*P* value*
		Time 1	Time 2	
Total stress-related behavior	Treatment	5 (0–8)	4 (0–8)	< 0.001
	Environmentally matched	4 (0–8)	3 (0–7)	0.078
Behavioral summation category				
Frenetic	Treatment	3 (0–6)	2 (0–5)	< 0.001
	Environmentally matched	2 (0–6)	2 (0–5)	0.13
Freeze	Treatment	3 (0–5)	2 (0–4)	0.008
	Environmentally matched	2 (0–5)	2 (0–4)	0.12
Fractious	Treatment	1 (0–2)	1 (0–2)	0.28
	Environmentally matched	1 (0–3)	1 (0–2)	0.083

Scores are represented as median (range).
*Wilcoxon signed rank test.
See Table 1 for remainder of key.

Discussion

Results of the present study indicated that trazodone administration decreased the expression of signs and behaviors associated with stress in hospitalized dogs. Trazodone-treated dogs and environmentally matched dogs were observed ≤ 45 minutes after initial trazodone administration for the treated dog (time 1) and again approximately 90 minutes later (time 2). Dogs that received trazodone had fewer stress-related signs or behaviors at time 2 than at time 1. Similarly, fewer frenetic and freeze behaviors were observed in these dogs at time 2 than at time 1. No change was noted in fractious behaviors; however, in the authors' experience, animals with fractious behaviors are infrequently admitted for hospitalization owing to safety concerns for the staff and students at the study facility, and the low frequency of these behaviors may have contributed to the lack of significant differences. In examining individual signs of stress, trazodone treatment was significantly associated with a reduction in lip licking, panting, and whining at time 2, compared with time 1, whereas expression of these signs did not differ between observation times for environmentally matched dogs that did not receive trazodone. It has been shown that lip licking and panting are positively correlated with salivary cortisol concentrations and thus may be useful behavioral indicators for changes in physiologic measures of stress.[15]

To better determine the effects of trazodone on stress in hospitalized animals, changes in stress-related behaviors were assessed for the treatment and environmentally matched groups individually (with each dog serving as its own control) as well as combined, through a statistical model that used behavioral data from the environmentally matched dogs to account for environmental effects on changes observed in treatment group dogs. When the latter model was used, trazodone treatment was significantly associated with a reduction in panting and in frenetic behaviors, but it was not associated with changes in freeze or fractious behaviors or in total stress-related behaviors. It is possible that the decrease in expression of frenetic behaviors in treatment group dogs reached statistical significance because of the low expression of frenetic behaviors in environmentally matched dogs at time 1, considering that the data for both groups were used to evaluate this outcome. This form of selection bias could be addressed with a randomized, controlled clinical trial of the drug in dogs that have similar signs of stress at baseline; with such a study design, randomly selected dogs not receiving the medication could serve as appropriate controls for trazodone-treated dogs. It is important to recognize that the environmentally matched dogs, although not receiving trazodone, were not true controls for the treated dogs in this study. Additionally, where multiple comparisons were made between groups and within groups for variables of interest without *P* value adjustments, the chance of a type I error was increased in the present study.

Stress in hospitalized dogs is considered to have strong environmental components.[15,21] Environmentally matched dogs were included in the present study to account for possible environmental effects on observed behavior of the trazodone-treated dogs. To control for differences in housing environments between treatment and environmentally matched dogs, we used a predetermined rubric to ensure environmental proximity and housing similarity for each pair of dogs on the basis of ward location of treatment group animals. Environmentally matched dogs were in an equivalent housing environment, such as the same ward or a similar type of housing (cage vs kennel run) in an environmentally equivalent ward, to that of treated dogs for 57 of 60 (95%) pairs. Therefore, it was expected that environmental effects on stress would be similar between the groups. Treatment group dogs were selected by the admitting clinician on the basis of behaviors observed on initial examination or while hospitalized. Because environmentally matched dogs were chosen as controls for environmental factors and were not selected as controls for the treated dogs, consideration was not made for the surgical status or duration of stay prior to study inclusion, and both of these factors differed significantly between the 2 groups.

In a study[17] of dogs hospitalized for elective surgery, investigators reported that panting and oral behaviors (snout licking and lip smacking) were observed prior to surgery in most of the 41 patients that were monitored.[17] Reduced occurrences of communicative behaviors (mouth opening and lip licking), potentially resulting from opioid administration, have also been observed in dogs after surgery (on the same day as the procedure), compared with observations for the same dogs prior to surgery.[18] The higher proportion of dogs evaluated before surgery in the trazodone treatment group, compared with the environmentally matched group, may have resulted in greater expression of stress-associated signs and behaviors observed in these dogs at time 1 and a greater appreciable change in these signs between times 1 and 2. Similarly, the higher proportion of postoperative patients in the environmentally matched group may have influenced the ability to detect changes in the variables of interest at time 2. Future studies should consider the surgical status of animals examined as part of the rubric for choosing control dogs in a clinical trial.

Duration of time in a novel environment can affect expressions of behavior.[9,11,12] Animals can acclimate to environmental stressors, which can decrease the expression of behavioral signs of stress.[24] From a clinical perspective, it follows that dogs with signs of stress that would warrant treatment with an antianxiety medication would have been identified early in their hospital stay; however, duration of stay was not considered in selecting environmentally matched dogs in the present study. It is possible that the lack of significant decreases in stress-related behaviors in environmentally matched dogs at time 2 resulted from the fact that they had been in the hospital longer than treatment group dogs and had already begun to acclimate to the environment. Results of 1 study[9] showed that healthy Beagles examined in a hospital setting 2 days after hospitalization had physiologic indicators of stress that were not present after 5 or 12 weeks in that same hospital environment, suggesting that > 2 days and < 5 weeks is needed for dogs to

acclimate to the hospital environment. The mean duration of stay for environmentally matched dogs was 2.2 days; therefore, although it was possible, we consider it unlikely that acclimation to the environment caused the lack of significant decreases in expression of stress markers in this population of dogs.

Dogs of the environmentally matched group in the present study had fewer stress-related signs and behaviors at time 1 than did treatment group dogs. It is possible that the trained observer may have been able to identify which dogs had been selected for trazodone treatment at time 1 because of their stress-related behaviors (which would have led to their selection for treatment), despite the methods used to blind the observer to patient treatment status. Almost every dog observed in the study had some stress-related behaviors, decreasing the likelihood of inadvertent identification by the observer, but a placebo-controlled clinical trial in which all dogs had similar signs at baseline would be needed to appropriately address this concern. Additionally, such a study design would allow baseline observations to be performed prior to medication administration, rather than following it, and administration of a sham treatment in a palatable treat would help to prevent any confounding effects created by association of a palatable food item with a hospital staff member. Future studies to examine recovery following discharge of dogs that did and did not receive trazodone while hospitalized would then be a logical next step to assess the effects of anxiety mitigation during hospitalization on recovery after hospitalization.

Adverse effects associated with oral administration of trazodone include soft feces or diarrhea, vomiting, constipation, excessive thirst, signs of anxiety or agitation, vocalization, drowsiness, panting, somnolence, urinary incontinence, behavioral disinhibition, and aggression.[43,44] Aggression associated with oral trazodone administration has previously been reported in 1 canine patient[44]; however, aggression was also observed as a transient adverse effect of IV trazodone administration in 3 of 6 dogs in another study,[47] and it was the only adverse effect observed following oral administration of the drug in the present study. Because of safety concerns, it is prudent to ensure hospital staff and dog owners are aware that trazodone administration can have this effect in some dogs.

In dogs, trazodone has previously been administered with antihistamines (diphenhydramine and hydroxyzine), topical insecticides (fipronil or imidacloprid), heartworm prophylactics (ivermectin, selamectin, and milbemycin), NSAIDs (carprofen, deracoxib, tepoxalin, firocoxib, and meloxicam), antimicrobials (cephalexin, cefpodoxime, amoxicillin, amoxicillin–clavulanic acid, clindamycin, rifampin, marbofloxacin, and metronidazole), sedatives (acepromazine), benzodiazepines (alprazolam, lorazepam, and clorazepate), and other systemic (gabapentin, amantadine, and prednisone) and topical treatments (triple antimicrobial ointment, chlorhexidine, and chlorhexidine-ketoconazole).[43,44] In the present study, trazodone was also administered with opioids, gastroprotectants, mirtazapine, and fenbendazole. To our knowledge, there have been no reported adverse events in dogs with concomitant administration of these medications and trazodone. Trazodone affects central serotonin receptors; therefore, use of trazodone with other serotonin enhancing medications, including other behavior-modifying medications and tramadol, has the rare possibility of causing serotonin syndrome or toxicosis.[52–55] Trazodone is routinely combined with other serotonin enhancing medications in people; however, individual reports of serotonin toxicosis exist.[56–59] Trazodone has been administered to dogs with other serotonin enhancing medications, including tricyclic antidepressants, selective serotonin reuptake inhibitors, azapirones, and tramadol, without reported adverse effects.[43,44] It is contraindicated to administer trazodone in combination with a monoamine oxidase inhibitor because this combination has a higher likelihood of causing serotonin toxicosis.[35] To our knowledge, serotonin toxicosis has not been reported in dogs with concomitant use of trazodone and non–monoamine oxidase inhibitor serotonin-enhancing medications; however, it should be on the differential diagnosis list if dogs receiving such medications develop signs consistent with toxicosis, such as hyperthermia, tremors, or seizures.[52] We recommend that clinicians unfamiliar with combined use of serotonin enhancing medications contact a board-certified veterinary behaviorist with any questions or concerns prior to prescribing these medications.

It is expected that most canine patients entering a veterinary hospital will have some signs of fear and anxiety.[23] Dogs manifest anxiety in different ways. Frequently these behaviors are missed, not recognized as being a response to stress, or attributed to some other motivation. Understanding that stress and anxiety drive some types of behavioral expression is critical to improving the care and welfare of these patients. Patients with fractious behaviors are often identified quickly and readily; however, freeze behaviors might be overlooked in a veterinary setting, and frenetic behaviors could be misinterpreted as typical for a certain breed or age or as evidence of an overly active patient, resulting in poor welfare for dogs that are stressed. Regardless of the category, hospitalized dogs with behavioral signs of stress after the initial few hours of acclimation may benefit from trazodone administration. It is important that clinicians take the individual patient's physical health and debilitation status into account when making decisions regarding antianxiety treatment, just as they would in the selection of pain management drugs, including the assessment of physiologic data and monitoring for adverse effects.

Reducing stress in hospitalized patients should be a standard of care in veterinary medicine. Clinicians should strive to mitigate stress for the welfare of their patients and the potential health benefits that such intervention might promote. The standard use of acepromazine, a sedative medication with negligible anxiolytic benefits, in stressed dogs may be detrimental to the behavioral and physical health of those dogs. As such, it is recommended by the authors that acepromazine no longer be the first choice in managing stressed hospitalized patients, just as it has been recommended that acepromazine not be the first choice for treatment of dogs with signs of stress

associated with car travel[60] or of dogs that require postoperative confinement.[44] In the present study, trazodone treatment was associated with reduction in specific stress-related signs and behaviors in hospitalized dogs and appeared to be well tolerated over a wide dose range and with a variety of concomitant medications. These results suggested that trazodone can alleviate stress in hospitalized dogs, and the findings of this study, together with studies by Gruen et al,[43,44] indicate that improvement in stress-related behaviors can be seen ≤ 90 minutes after trazodone administration.

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Footnotes

a. Trazodone hydrochloride, Qualitest Pharmaceuticals, Huntsville, Ala.
b. Greenies Pill Pockets, The Nutro Company, Franklin, Tenn.
c. Stata, version 12.1, StataCorp LP, College Station, Tex.

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Appendix

Descriptions of stress-related signs or behaviors used in evaluation of 117 dogs (59 trazodone-treated dogs and 58 environmentally paired dogs that did not receive trazodone) in a study to assess effects of the drug on behavioral signs of stress in dogs admitted to a veterinary teaching hospital.

Sign or behavior	Description
Lifting a forelimb	Lifting one forelimb off of the ground in response to presence of stimulus (eg, person, dog, or object).
Pupil dilation	Any dilation of the pupils (should be bilateral).
Lip licking	Tongue licking around any portion of the lips or flicking out of the mouth and back in.
Pacing	Walking back and forth, from front to back or side to side of the cage or kennel.
Panting	Increased respiratory rate with the mouth open or shut. If the mouth is open, tongue often extends out of the mouth.
Spinning	Turning in circles in the cage or kennel.
Trembling	A portion of the body or the entire body shaking or quivering, not as an active body movement by the dog.
Wet dog shake	Shaking the head, body, or both from side to side as if the dog just came out of the bath tub, without the dog being wet.
Whining	High-pitched sound made intermittently or continually from the mouth or through the nose.
Yawning	Opening the mouth wide. Sometimes the tongue will come out or curl towards the roof of the mouth, and the dog will often take in and let out a deep breath without conscious effort.
Averting gaze	Moving the eyes or turning the head away; actively avoiding looking at an object, a person, or a dog that otherwise the dog would be looking at directly.
Pinning back ears	In erect-eared dogs, lowering pinnae to the side or to the back, sometimes flat against the head or neck. In floppy-eared dogs, moving the pinnae back against the sides of the face or neck.
Whale eye sign	Eyelids are wide open so the sclera is easily seen all around the eye or to the side (medial or lateral).
Growling	Low, rough sound that tends to vibrate in the dog's neck or chest.
Lunging	Moving forward toward a stimulus (person, dog, or object) with intent and sudden force.
Showing teeth	Retracting or curling of the lips in such a way that teeth are visible (often only the upper teeth and sometimes only canine teeth), with apparent intent to warn away.
Snapping	Mouth is opened and closed rapidly, with teeth hitting each other as the jaw rapidly closes.