Efficacy of a single dose of trazodone hydrochloride given to cats prior to veterinary visits to reduce signs of transport- and examination-related anxiety

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OBJECTIVE
To evaluate the efficacy of a single dose of trazodone for reducing anxiety in cats during transport to a veterinary hospital and facilitating handling during veterinary examination.

DESIGN
Double-blind, placebo-controlled, randomized crossover study.

ANIMALS
10 healthy client-owned cats (2 to 12 years of age) with a history of anxiety during transport or veterinary examination.

PROCEDURES
Each cat was randomly assigned to first receive trazodone hydrochloride (50 mg) or a placebo PO. The assigned treatment was administered, and each cat was placed in a carrier and transported by car to a veterinary clinic, where it received a structured veterinary examination. Owners scored their cat's signs of anxiety before, during, and after transport and examination. The veterinarian also assessed signs of anxiety during examination. After a 1- to 3-week washout period, each cat received the opposite treatment and the protocol was repeated.

RESULTS
Compared with placebo, trazodone resulted in a significant improvement in the cats' signs of anxiety during transport. Veterinarian and owner scores for ease of handling during veterinary examination also improved with trazodone versus the placebo. No significant differences were identified between treatments in heart rate or other physiologic variables. The most common adverse event related to trazodone administration was signs of sleepiness.

CONCLUSIONS AND CLINICAL RELEVANCE
Oral administration of a single dose of trazodone to cats prior to a veterinary visit resulted in fewer signs of transport- and examination-related anxiety than did a placebo and was generally well tolerated by most cats. Use of trazodone in this manner may promote veterinary visits and, consequently, enhance cat welfare. (*J Am Vet Med Assoc* 2016;249:202–207)

Veterinary visits by cats in the United States decreased 14% from 2001 to 2011, as reported by the AVMA.[1] In the Bayer Veterinary Care Usage Study,[2] owners reported cat resistance to carriers and transport-related anxiety as well as stressful events at the veterinary clinic as major deterrents to veterinary visits. The reduced number of veterinary visits negatively impacts the health and welfare of cats as well as the financial bottom line of veterinary practices.

Wellness visits when cats are apparently healthy provide opportunities for delivering best care in terms of diet, vaccines, and behavior. Health problems can be identified early in their course to optimize treatment success. If cats are not brought for veterinary visits on an annual or more frequent basis, then by the time a need for veterinary care is identified by owners, existing disease processes can be more advanced and treatment more complicated and costly.

Further complicating the situation, when cats with signs of anxiety are brought for veterinary visits, they may physically resist a comprehensive examination and risk injury to veterinary personnel, clients, and themselves. Vital signs and laboratory test results may reflect the effects of distress and be difficult to interpret.[3,4] In addition, each veterinary visit associated with anxiety and distress may condition cats to expect that future visits will be similar.[4]

Many veterinarians are actively working to make veterinary visits less stressful for cats. Feline-friendly waiting and examination rooms provide a more pleasing environment for cats than traditional rooms do. Behavioral interventions, such as conditioning cats to carriers,[5] can reduce signs of transport-related anxiety, and low-stress handling can reduce signs of veterinary examination–related anxiety. In addition to these techniques, a safe, effective, and easy-to-administer single-dose medication

for cats for reduction of stress associated with veterinary visits would be an important advantage.

Pharmacological agents that may be used to overcome the distress of carrier confinement, transport, and veterinary examinations are limited for cats. Several types of tranquilizers or sedatives are available by prescription, but all have disadvantages. Orally administered acepromazine maleate[6] or diazepam[6] and oromucosally applied dexmedetomidine gel (with or without buprenorphine hydrochloride)[7] have been proposed. However, the potential adverse effects of these agents limit their usefulness prior to transport for veterinary visits. For example, acepromazine is associated with paradoxical excitation in cats and dexmedetomidine is associated with vomiting following administration,[8] whereas more serious hepatic necrosis may follow oral administration of diazepam.[9]

Various over-the-counter treatments are available, such as L-theanine or synthetic feline pheromone sprays or diffusers,[10] although anxiolytic effects in cats during veterinary examination have not been demonstrated. The purpose of the study reported here was to evaluate the efficacy of oral administration of a single dose (50 mg) of the drug trazodone hydrochloride to cats to reduce signs of anxiety during transport to the veterinary clinic and during veterinary examination. Classified as a serotonin antagonist and reuptake inhibitor, trazodone has been used successfully in dogs for its anxiolytic and mild sedative properties.[11,12] In a small sample of laboratory cats, a single dose of trazodone at 50, 75, or 100 mg PO appeared to be well tolerated and resulted in a considerable sedative effect.[13] We hypothesized that when given to client-owned cats prior to veterinary visits, trazodone would reduce signs of transport-associated anxiety and facilitate veterinary examination. We also predicted that there would be no difference in values of certain physiologic variables between trazodone and a placebo.

Materials and Methods

Animals

Cats evaluated at North Carolina State University Veterinary Health and Wellness Center and identified as in good health and between 2 and 12 years of age were considered for inclusion in the study. Cats were required to have ≥ 1 behavioral sign consistent with transport- or veterinary examination–associated anxiety. Owners of qualifying cats were required to have signed a consent form, be able to orally administer medication, be willing to assess their cat's behavior by use of specific criteria, and live within a 10- to 30-minute drive to the center. In addition, owners had to be willing to transport their cats to the center in a cat carrier for 2 visits 1 to 3 weeks apart. All study protocols were approved by the North Carolina State University Institutional Animal Care and Use Committee.

Procedures

A simple randomization table, produced by the North Carolina State Pharmacy, was used to assign the order of treatment to cats. Cats were randomly assigned to first receive a 50-mg tablet of trazodone hydrochloride[a] or a placebo. A single dose of trazodone or placebo was dispensed prior to the first visit. Owners, blinded to treatment identity, were instructed to orally administer the provided treatment in a manner that would be best tolerated by their cat (ie, hidden in canned cat food, hidden in a malleable treat,[b] or directly administered PO). The placebo was a sodium bicarbonate tablet identical in appearance to trazodone. The second dose of medication (trazodone or placebo) was dispensed at the end of the first visit.

Approximately 1 to 1.5 hours after treatment administration at home, owners placed their cat in a travel carrier and brought it by car to the veterinary clinic. After a brief wait in the lobby (approx 1.5 to 2 hours after treatment administration), each owner and cat were escorted to a designated examination room and a physical examination was performed by a veterinarian (BJS) and technician (LBH), both of whom were blinded to treatment received. The examination concluded approximately 2 to 2.5 hours after treatment administration. One to 3 weeks later, owners were instructed to orally administer the second provided treatment (trazodone or placebo) and returned with their cat to the veterinary clinic for a second visit. The same protocol was followed for both visits.

Assessments

Cats were assessed for signs of anxiety and fear at specific points by use of 3 scoring systems: the McCune cat stress score,[14] the behavioral response score (modified from Rand et al),[3] and the tractability score.[15] Owners used a standard form to assign cumulative stress scores to their cat at the following points: before transport, during transport, after transport while in the clinic waiting room, during the examination, and immediately after the examination. The veterinarian assigned a cumulative stress score for the entire examination (1 = fully relaxed, 2 = weakly relaxed, 3 = weakly tense, 4 = very tense, 5 = fearful or stiff, 6 = very fearful, and 7 = terrorized).[14] In addition to recording these scores, owners were asked to report for each assessment point the presence or absence of objective signs associated with anxiety, including urination, defecation, anal gland release, vomiting, excessive salivation, trembling, open-mouth breathing, and vocalization. Intensity of vocalization was also scored (0 = absent, 1 = mild, 2 = moderate, and 3 = severe).

For the veterinary examination, each cat was handled in a prescribed order by the same veterinarian (BJS) and assisted by the same technician (LBH) in the presence of each owner. The cat's carrier was placed on the floor of the examination room, and the carrier door was opened to allow the cat to voluntarily exit. If the cat exited the carrier of its own volition, it was allowed to explore the examination room briefly, then was placed on the examination table, which was covered with a nonslip rubber mat. If the cat did not voluntarily exit the carrier, the carrier was placed on

the examination table, the top of the carrier was removed, and the cat was gently lifted onto the table. If the carrier top could not be removed, the cat was gently extracted from the carrier and placed on the examination table.

The veterinary examination consisted of 12 veterinary procedures and was typically completed within 20 minutes. These procedures included removal of the cat from the carrier; placement on the examination table; weighing on a tabletop scale; visual examination of the head, eyes, and oral cavity without instrumentation; thoracic auscultation and measurement of heart and respiratory rates; abdominal palpation; lymph node palpation; measurement of aural temperature; direct ophthalmoscopic examination; otoscopic examination; shaving of a small section of hair at base of tail and Doppler ultrasonographic determination of arterial blood pressure; and release after examination. Behavioral data following each of the 12 procedures and for the examination overall were assigned by the veterinarian by use of the behavioral response score system[3] (0 = absent, 1 = mild, 2 = moderate, 3 = severe, and 4 = too severe to complete), which involved scoring 4 specific cat behaviors at each assessment point: vocalization (whimper, cry, or meow), struggling or attempts to escape, aggression (except for hissing or growling; ears flattened back, tail lash, or batting), and severe aggression (biting, attacking, and hissing and growling).

Physiologic and behavioral data were collected by the veterinarian during the examination. Physiologic data included heart rate, respiratory rate, aural temperature, and Doppler ultrasonographic measurement of arterial blood pressure.

At the conclusion of the veterinary examination, both the veterinarian and owner independently assigned a tractability score,[15] which was based on the ease by which the veterinarian could perform each examination procedure and the appearance of the cat (0 = cat completely relaxed, 1 = easy to examine but not entirely relaxed, 2 = relatively easy to examine, 3 = restraint needed to examine safely, 4 = very difficult to examine, and 5 = unable to examine).

At the conclusion of each visit and to understand owner perception of their cat's anxious behavior, owners were asked to speculate whether their cat received the placebo or trazodone. After each visit, in a survey sent via email, owners were asked to report any adverse events noted within 24 hours after administration of the test drug.

Statistical analysis

Data were entered into an electronic data collection system[c] and exported for statistical analysis. Because of the small sample size and the nature of the collected data, nonparametric statistical tests were used. Owner assessments of cat behavior and anxiety level at each assessment point were compared between trazodone and placebo by use of the McNemar test. Vocalization scores were compared between treatments by use of the Wilcoxon signed rank test. Physiologic variables were compared between treatments by use of the Wilcoxon signed rank test. Veterinarian-assigned behavioral scores for each procedure were summed and compared between treatments by use of the Wilcoxon nonparametric test to determine whether the paired differences were equal to 0. Veterinarian- and owner-assigned tractability scores were collapsed into 2 categories—relaxed (scores of 0, 1, and 2) and tense (scores of 3, 4, and 5)—and compared between treatments by use of the McNemar test. Sample size was 10 cats for all tests unless stated otherwise. Values of $P < 0.05$ were considered significant.

Results

Animals

Thirteen exclusively indoor cats (5 neutered males and 8 spayed females) were originally enrolled in the study. Mean age was 6.6 years (range, 2.0 to 12.4 years), and mean body weight was 4.5 kg (9.9 lb; range, 3.3 to 6.5 kg [7.3 to 14.3 lb]). Ten cats (3 neutered males and 7 spayed females) completed the study. Their mean body weight was 4.6 kg (10.1 lb; range, 3.3 to 6.5 kg), and mean age was 6.8 years (range, 2.1 to 10.7 years).

Of the 3 cats that did not complete the trial, 1 cat became ill after enrollment but before participation and was withdrawn per recommendation of its primary care veterinarian. The second cat became ill between the first and second veterinary visit (illness unrelated to the study protocol) and was consequently withdrawn. That cat was later found to have small bowel lymphoma. The third cat was withdrawn by the owner on the basis of an adverse event that was noticed at home 20 minutes after trazodone administration. This owner reported that the cat had vocalized and appeared agitated at the time but subsequently fully recovered. By arrangement, this cat was physically examined (BJS) several weeks after the incident, and no gross abnormalities were detected. A CBC and serum biochemical analysis were performed; all findings were within reference limits.

All cats were reported by their owners to have had at least one of the evaluated signs of anxiety (ie, urination, defecation, anal gland release, vomiting, excessive salivation, trembling, open-mouth breathing, or escape attempts) during transport in a carrier in the past. Eight cats were reported by their owners to have had at least one of the evaluated signs of anxiety during veterinary examination in the past (ie, vocalization, struggle, escape attempt, or mild or severe aggression).

Study treatments were administered PO to 4 cats in malleable treats, to 4 cats hidden in canned food, and to 2 cats by direct administration by hand. All owners reported that their cats received the total amount of the medication. On the basis of body weight, trazodone doses ranged from 7.7 to 15.2 mg/kg (3.5 to 6.9 mg/lb).

Owner assessments

During the study, few cats had one or more of the evaluated signs of anxiety before transport, during transport, after transport, during examination, and af-

ter examination, as reported by their owners. No cats released their anal glands. Because the signs of anxiety occurred too infrequently for statistical analysis, only descriptive statistics are provided for this particular type of assessment.

After receiving trazodone or the placebo, no cats had any of the evaluated signs of anxiety. Stress scores assigned before transport (after treatment administration 1 to 1.5 hours earlier) were significantly lower for trazodone than for the placebo (McNemar test, $P = 0.02$).

During transport, 3 cats had 1 or more of the evaluated signs of anxiety. One cat urinated and defecated after receiving the placebo and urinated after receiving trazodone. The second cat vomited, had hypersalivation, trembled, and breathed with an open mouth after receiving the placebo. The third had open-mouth breathing after receiving the placebo. Stress scores assigned during transport did not differ significantly between treatments **(Figure 1)**.

After transport while in the waiting room, no cats had any evaluated sign of anxiety after receiving trazodone; however, 1 cat urinated, defecated, excessively salivated, and had open-mouth breathing and another cat excessively salivated after receiving the placebo. Trazodone administration resulted in significantly (McNemar test, $P = 0.02$) lower cat stress scores at this assessment point than did placebo administration.

Ten cats vocalized before transport when given the placebo, and 7 cats vocalized when given trazodone; all except 1 cat had a reduction in their vocalization intensity score. Trazodone administration resulted in significantly (Wilcoxon signed rank test, $P = 0.008$) less frequent vocalization during transport than did placebo administration. Eight cats vocalized after transport when given the placebo, and 2 vocalized when given trazodone.

During the veterinary examination, no cats urinated, defecated, released their anal glands, vomited, excessively salivated, trembled, or had open-mouth breathing, regardless of treatment received. No cats vocalized. Trazodone administration resulted in significantly (Wilcoxon signed rank test, $P = 0.04$) lower stress scores during this period than did placebo administration. Owner-assigned tractability scores during the examination were significantly ($P = 0.03$) more favorable with trazodone versus the placebo (Figure 1).

After the veterinary examination, no cats urinated, defecated, released their anal glands, vomited, excessively salivated, trembled, or had open-mouth breathing, regardless of treatment received. Trazodone administration resulted in significantly (Wilcoxon signed rank test, $P = 0.008$) lower stress scores during this period than did placebo administration.

Although blinded to treatment, 9 of 10 owners correctly identified the treatment their cats received after observing their behavior during transport and examination.

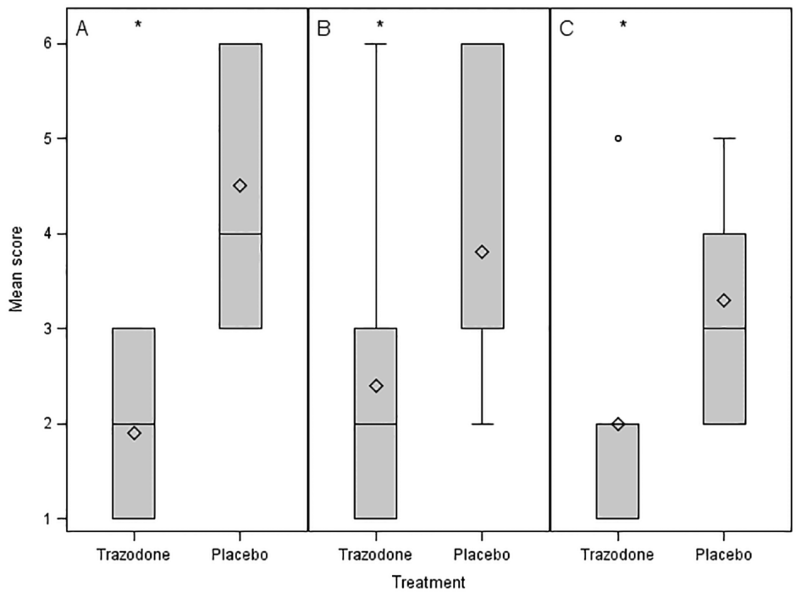

Figure 1—Box-and-whisker plots of mean owner-assigned stress scores[14] (A) for their cat during transport by car to a veterinary visit (A) and owner-assigned (B) and veterinarian-assigned (C) tractability scores[15] for the same cat during a veterinary examination. Before transportation to the veterinary hospital, cats received a single dose of trazodone hydrochloride (50 mg) or placebo in a crossover study design with 1 to 3 weeks separating treatments. Stress scores were assigned as follows: 1 = fully relaxed, 2 = weakly relaxed, 3 = weakly tense, 4 = very tense, 5 = fearful or stiff, 6 = very fearful, and 7 = terrorized. Tractability scores were assigned as follows: 0 = cat completely relaxed, 1 = easy to examine but not entirely relaxed, 2 = relatively easy to examine, 3 = restraint needed to examine safely, 4 = very difficult to examine, and 5 = unable to examine. Each box represents the range between the 25th and 75th percentile. The horizontal line within each box represents the median, and the diamond represents the mean. Whiskers represent minimum and maximum values. An outlier is indicated by the circle. *Value differs significantly ($P < 0.05$) between treatments.

Veterinary assessments

All physiologic values for all cats were within reference ranges after trazodone and placebo administration. No significant differences were identified between trazodone and placebo with respect to heart rate ($P = 0.55$), blood pressure ($P = 0.91$), or aural temperature ($P = 0.24$). Respiratory rate was lower, albeit nonsignificantly ($P = 0.055$), after trazodone versus placebo administration.

Overall, behavioral scores as assigned by the veterinarian were significantly (Wilcoxon signed rank test, $P = 0.006$) lower for cats after receiving trazodone versus the placebo. Trazodone administration resulted in significantly (Wilcoxon signed rank test, $P = 0.01$) more favorable tractability scores than did placebo administration, with cats considered relaxed versus tense after receiving trazodone (Figure 1). For all components of the veterinary examination, trazodone administration

resulted in significantly (McNemar test, $P = 0.03$ for each comparison) lower stress scores before, during, and after veterinary examination.

Adverse events

In response to the email survey after the veterinary visit, owner reports of adverse events were limited to 1 report of transient sleepiness. No vomiting, diarrhea, or other behavioral changes were reported.

Discussion

The present study revealed that trazodone may be useful for cats in the amelioration of signs of anxiety associated with transport or veterinary visits. Many cat owners view veterinary visits as a negative experience because their cats appear frightened by the visits.[2] This perception may lead to a decrease in veterinary visits for cats, which would adversely impact the ability of veterinarians to provide wellness care and early disease detection for their feline patients, thereby impacting cat welfare.

Trazodone administration to cats in the study reported here resulted in a significant decrease in the severity of anxiety-related signs without affecting physiologic variables or causing excessive sedation. Therefore, administration of trazodone to cats prior to transport and veterinary examination may promote veterinary visits by making the experience less anxiety-producing for cats and more pleasant for their owners. This strategy may also enhance the bond between cats, owners, and veterinarians.

The low number of cats that had specific anxiety-related signs during transport in the present study precluded statistical comparison of their frequency between trazodone and the placebo. However, cats that received the placebo generally had more anxiety-related signs than did cats that received trazodone. Six of 7 cats that had anxiety-related signs during transport when given the placebo did not have them when given trazodone. After transport, 9 of the 10 cats had anxiety-related signs when given the placebo, whereas only 3 of the 10 cats had them when given trazodone.

Cats also vocalized less when given trazodone, compared with when given the placebo. This decrease was evident before, during, and after transport. Distress vocalizations during transport can upset cat owners and be distracting while driving, and such vocalizations in the veterinary waiting room are disruptive to people and other pets. Cat owners who participated in the study reported that the decrease in their cat's vocalizations during transport was an important indication of improvement in their cat's level of distress. We believe the positive effect of trazodone on distress vocalizations was an important outcome that could lead to owners being more likely to transport their cats to a veterinary clinic for wellness care.

Most striking were the examination findings in which cats had improved behavioral and tractability scores when given trazodone instead of the placebo. In fact, all cats but 1 had a positive response to trazodone in this regard. That cat was scored as fearful when given the placebo and very fearful (a worse score) when given trazodone. Because anxious cats without treatment may be fearful or very fearful for veterinary visits, this particular cat's behavior may have represented a lack of response to trazodone or a paradoxical response.

Findings of the present and a previous laboratory investigation[13] suggested that trazodone is generally well tolerated by healthy cats. Other than 1 unusual unexplained but transient behavioral reaction by 1 cat after ingestion of trazodone in its food (causing its owner to withdraw it from the study), no serious adverse events associated with trazodone administration were reported. A few owners mentioned transient sleepiness or partial prolapse of the nictating membrane, but we did not consider these events to be serious. Indeed, several cat owners who participated in the study requested trazodone for their cat for subsequent veterinary visits.

In contrast to the behavioral effect of trazodone on anxiety reduction and ease of handling, trazodone did not have a significant effect on measured physiologic variables. Consequently, trazodone administration at 50 mg PO did not interfere with measurement of heart rate, respiratory rate, aural temperature, or blood pressure during the examination, which were all within reference limits for both treatments. We speculate that the nonsignificantly lower respiratory rate observed when cats were given trazodone instead of the placebo may have been an indicator of less anxiety. A larger sample size would be necessary to more fully evaluate this effect.

When owners were asked to speculate whether they believed their cat had received trazodone or the placebo prior to the veterinary visit, all owners but 1 were correct in their perception. Owner scores for tractability during examination also improved when cats were given trazodone. We surmised that this was because owners could recognize the absence of specific behaviors, such as vocalizations, that they associated with their cat's anxiety level or they noticed improvement of signs included in the stress scoring system, which was initially used for shelter or feral cats[15] but has since been adapted for clinical use. Recognizing that many owners view veterinary examinations as stressful,[2] we interpreted this as a beneficial effect of trazodone. We believe that the tractability scoring system[15] used was clinically relevant and meaningful to owners and veterinarians. Owner perception of the cat's stress level is important to understand to achieve compliance with wellness visits.

In the small clinical study reported here, oral administration of a single 50-mg dose of trazodone to healthy cats appeared to improve the experience of going to the veterinary clinic, from entering the carrier to transport through to veterinary examination. Findings suggested that trazodone can be administered by owners at home prior to veterinary visits and used to promote regular veterinary visits, which will enhance the health and welfare of cats.

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Footnotes

a. Teva, North Wales, Pa.
b. Pill Pockets, Nutro Co, Franklin, Tenn.
c. Medrio Electronic Data Capture, San Francisco, Calif.

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