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The Use of Trazodone to Facilitate Post-Surgical Confinement in Dogs

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Abstract

Objective—To investigate the safety and efficacy of the oral serotonin antagonist/reuptake inhibitor trazodone hydrochloride to facilitate confinement and calming after orthopedic surgery in dogs.

Design—Prospective open-label trial.

Animals—36 client-owned dogs.

Procedures—Healthy dogs were recruited when presented for pre-surgical evaluation for orthopedic procedures. Starting the day after surgery, dogs were administered trazodone (~3.5 mg/kg, *per os* (PO), q12h) with tramadol (4–6 mg/kg, PO, q8–12h) for pain management. After 3 days, tramadol was discontinued and trazodone was increased (~7 mg/kg, PO, q12h) and maintained for at least 4 weeks. If needed, trazodone dosage was increased to 7–10 mg/kg, PO, q8h. Clients completed electronic surveys rating their dogs' confinement tolerance, calmness/hyperactivity level, and responses to specific provocative situations, prior to surgery and at 1, 2, 3, and 4 weeks and at the post-surgical evaluation (8–12 weeks).

Results—The majority of clients (~90%) reported that, when given trazodone during the 8–12 weeks following orthopedic surgery, their dogs improved moderately or extremely with regard to confinement tolerance and calmness. Trazodone was well tolerated, even in combination with non-steroidal drugs, antibiotics, and other medications; no dogs were withdrawn from the study due to adverse reactions. Client-reported median onset of action of trazodone was 31–45 minutes and median duration of action was four or more hours.

Conclusions and Clinical Relevance—The results suggest that oral trazodone is a safe and efficacious medication that may be used to facilitate confinement and enhance behavioral calmness of dogs during the critical recovery period following orthopedic surgery.

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Introduction

For optimal treatment success of elective orthopedic surgeries in dogs, such as stifle stabilization following cranial cruciate ligament tear, effective post-surgical management is critical. Typical management includes a 6–12 week post-surgical period of confinement and exercise restriction. Because patients may be young,[1] active, healthy, and unaccustomed to confinement, implementation of post-surgical instructions is often challenging to clients. Failure to comply with activity restriction may lead to protracted recovery or even surgical treatment failure, necessitating a second surgical procedure.[2]

Historically, the phenothiazine tranquilizer acepromazine maleate,[a] has been used to facilitate confinement, but this agent may produce excessive sedation[3] and increase the risk of falling. Acepromazine may also cause paradoxical excitation and a range of physiological effects.[4] There is a need for a well-tolerated oral agent to facilitate confinement after orthopedic surgery without producing undesired side effects.

The atypical antidepressant trazodone hydrochloride[b] is a medication with a long track record of safe use in humans for the treatment of anxiety, depression, and to facilitate sleep, particularly in combination with selective serotonin reuptake inhibitors.[5] Trazodone is classified as a serotonin (5-HT) antagonist/reuptake inhibitor, with complex activity on serotonergic systems. In humans at low to moderate dosages, trazodone acts to antagonize postsynaptic $5HT_{2A}$ as well as histaminic and $alpha_1$ adrenergic receptors which may account for its moderate hypnotic effects.[6] At higher dosages, trazodone also acts as an antagonist at postsynaptic $5HT_{2C}$ receptors.[6] Its active metabolite, m-chlorophenenylpiperazine is a potent direct 5-HT agonist. Trazodone has minimal effects on muscarinic cholinergic receptors, so has few anticholinergic side effects. In mammals tested, trazodone has a wide safe dosage range. The median lethal dosage ($LD_{50)}$ of trazodone *per os* (PO) is high: 610 mg/kg (277 mg/lb) in mice, 486 mg/kg (221 mg/lb) in rats, and 560 mg/kg (255 mg/lb) in rabbits.[7] To date, the LD_{50} in dogs has not been determined.

In humans, trazodone is generally well-tolerated at an oral dosage range from 150 to 600 mg/day,[8] alone and in combination with other drugs (excepting monoamine oxidase inhibitors for which concurrent use is contraindicated). Trazodone is commonly prescribed as a sleep aid for patients prescribed antidepressants in the selective serotonin reuptake inhibitor class. Trazodone has minimal if any effect on seizure threshold.[9] In its generic formulation, trazodone is widely prescribed. Based on prescription frequency, trazodone HCl was ranked 29th among the top 200 prescription drugs for 2010[10] with over 18 million prescriptions written for its use by physicians in the United States. The long history of safe use in humans, alone and in combination with other medications, suggest that trazodone may be a useful therapeutic agent in dogs.

In dogs, trazodone has been used in the treatment of anxiety disorders, alone or in combination with other behavioral medications.[11–12] The drug enhanced behavioral calmness and reduced anxiety thereby improving patient welfare with few side effects. A

[a]PromAce®, Fort Dodge Animal Health, Overland Park, KS.
[b]Desyrel®, Bristol-Myers Squibb, New York, NY.

recent single dose pharmacokinetic study of trazodone in six dogs, found that when given orally, trazodone produced mild sedation with no observable side effects.[13] In anesthetized dogs, trazodone has been shown to have very little effect on cardiac function, compared with equally effective dosages of imipramine.[14] These characteristics make trazodone an ideal agent to decrease anxiety, agitation, and distress associated with confinement in post-surgical dogs.

A pilot study suggested the usefulness of this strategy. Seventeen canine patients at the North Carolina State University College of Veterinary Medicine (NCSU-CVM) Veterinary Health Complex (VHC) were prescribed trazodone at a dosage range of ~3.5–7 mg/kg (1.6–3.2 mg/lb) q 12 h following orthopedic surgery.[15] A dose increase to ~8–10 mg/kg (3.6–4.5 mg/lb) q 12 h) was permitted. Using an on-line survey tool, clients were queried about their dog's behavior prior to the surgery and during the course of their surgical recovery. All dogs remained on the medication for a minimum of 4 weeks after surgery. No adverse effects were reported by any client, and no dogs were taken off of the medication due to any complications. Fifteen clients (88.2%) felt that the medication was helpful for their dog, while two clients (11.8%) felt that it was helpful after an increase in the initial dosage. Based on these results, the present study was developed to more fully evaluate the efficacy of trazodone for the purpose of facilitating post-surgical confinement and to evaluate the safety of this drug in a larger clinical trial.

Our hypothesis was that, per clients' assessment of their dogs' behavior, the use of trazodone would facilitate confinement and enhance behavioral calmness post-orthopedic surgery, and that trazodone would prove safe and efficacious for this purpose. An additional objective was to quantify clients' perception of onset and duration of action of trazodone in this context.

Materials and Methods

All procedures were approved by the NCSU Institutional Animal Care and Use Committee before commencement of the study, and informed consent was obtained from owners of all enrolled dogs. Dogs admitted to the NCSU VHC for orthopedic surgery were recruited into this study. Dogs were eligible for enrollment if they were in good health, weighed at least 5 kg (11 lb), and were not taking concomitant behavioral medications or monoamine oxidase inhibitors, such as amitraz products. Because of the rare side effect of priapism associated with trazodone use in humans[16] and to avoid any potential reproductive consequences, only castrated males and spayed females were enrolled. Prior to surgery, dogs were evaluated for general health by physical examination and routine laboratory assessment.

Clients were eligible to enroll their dogs if they agreed to administer medication as directed, report any adverse effects, and be responsible for completing a weekly on-line survey regarding features of their dog's behavior critical to post-orthopedic surgical management. In homes with multiple caregivers, one client was designated to complete the weekly surveys. All participating clients signed an informed consent form, and were provided with emergency contact information. At the time of enrollment, clients were asked by the study technician to complete a pre-surgical survey that evaluated their dog's behavior in response

to five provocative situations, relevant to successful post-orthopedic surgical management, and one temperament measure. The survey asked clients to rate their dogs' (1) tolerance of confinement when left alone, (2) tolerance of confinement when the client was at home, (3) tendency to pull on leash walks, (4) willingness to be controlled by the client using familiar commands, (5) intensity of greeting behavior to the client and other familiar persons, and (6) overall calmness. Lower scores reflected calmer, more manageable dogs.

After surgery, all clients were provided written emergency contact information and standardized instructions for post-surgical confinement and activity restriction for the following 4–12 weeks (depending on the specific surgery). Details of confinement varied from dog to dog, but generally consisted of a crate, small pen, or small room. Dogs were prescribed trazodone based on body weight, to be given twice daily PO for at least 4 weeks. For the first three post-surgical days, clients were instructed to administer trazodone at an "initiation dosage" (1/2 the standard dosage, approximately 3.5 mg/kg [1.6 mg/lb], PO, q 12 h) while giving the analgesic tramadol[c] (4–6 mg/kg [1.8–2.7 mg/lb], PO, q 8–12 h), a drug with serotonergic activity.[17] The low initiation dosage of trazodone was designed to begin to establish initial blood levels, develop tolerance to transient sedating effects of trazodone, and avoid the possibility of serotonin excess.[17] After 3 days, tramadol was discontinued, and trazodone was increased to the "standard dosage" (~7 mg/kg [3.2 mg/lb], PO, q 12 h). If, during the study, the standard dosage was considered by the client to be insufficient, after consultation with a veterinary behaviorist, the individual dosage and dosage schedule of trazodone was increased to a "high dosage," ~7–10 mg/kg [3.2–4.5 mg/lb], PO, q 8 h (thrice daily). For useful comparisons between the "standard" and "high" dosages, "total daily dosage" was calculated as the total amount of trazodone administered PO during a 24-hour period.

Per surgeon's prescription during the post-surgical period, any dog could receive other concomitant drugs PO or topically for a variable number of days to weeks including non-steroidal anti-inflammatories, buprenorphine, amantadine, or antibiotics. During the course of the study, dogs continued on routine heartworm and flea prophylaxis as directed by their primary veterinarian.

Data Collection

Each week for 4 weeks following surgery, clients were sent, via e-mail, a link to an on-line survey to evaluate their dog's post-surgical behavior. A final fifth survey was completed at the time of the final patient evaluation, 8–12 weeks after surgery. The surveys for post-surgical weeks 1, 2, 3, 4, and the final survey repeated questions on the pre-surgical survey. In addition, clients were asked to assess the usefulness of trazodone administration with regard to confinement tolerance and calming on a 4-point ordinal scale from "not at all helpful" to "extremely helpful." A low score was associated with greater confinement tolerance and calming.

On each survey, clients were asked to confirm the dosage and schedule of trazodone administered, the latency and duration of effect, as well as list any concomitant medications

[c]Ultram®, Janssen Pharmaceuticals, Inc., Titusville, NJ.

that were given. Clients were queried about adverse events in each survey in a free-text field, and were encouraged to contact study personnel at any point if they had questions or felt that the dog's trazodone dosage was inadequate. After 4 weeks on the medication, the study technician called each client by telephone to discuss the option to continue trazodone until the final 8–12 week post-surgical visit. At the final post-surgical visit, laboratory tests (complete blood count, chemistry profile) were collected for comparison to the pre-surgical laboratory values. As an incentive for completion of the surveys, costs of the trazodone and the post-surgical laboratory tests were covered by the study.

Withdrawal from Study

Clients were permitted to withdraw from the study at any time and for any reason. Surgeons and investigators could withdraw animals from the study if they were concerned about the health or comfort of the animal. Investigators could also withdraw animals if clients were non-compliant with the dosing and reporting requirements of the study.

Statistical Analysis

Data obtained from client rating scales were analyzed using non-parametric statistics, as noted in the text.[18] The Cochran-Mantel-Haenszel test was used for the analysis of ordinal data. The results from the final survey for each patient were used to evaluate overall response. Improvement was defined as change from baseline in a positive direction. The group of dogs that received trazodone thrice daily (high dosage) were compared to dogs that received trazodone twice daily (standard dosage) during the study to determine if there were differences in age, weight, or baseline ratings that might have identified these dogs *a priori.* Dogs were also classified by surgery type ("Hip", "Knee", or "Other") and groups were analyzed for differences in age, weight, total dose and schedule of trazodone. For all tests, a p-value of <0.05 was considered statistically significant. Unless otherwise noted, the sample size was 36 dogs. Descriptive statistics are expressed as mean ± standard deviation.

Results

Forty-one dogs were enrolled in this trial, 22 were castrated males, and 19 were spayed females. Thirty-six dogs completed the trial. Four dogs were withdrawn due to client non-compliance with on-line surveys and communications; one dog was withdrawn when it was determined he was concurrently receiving fluoxetine. No clients elected withdrawal and no dogs were withdrawn for adverse events. For the 36 dogs that completed the trial, the mean dog age was 3.0 years +/− 2.46 years and the mean dog weight was 32.0 ± 10.6 kg (70.4 ± 23.3 lb).

Surgeries

The forty-one dogs recruited for the study underwent a variety of elective orthopedic surgeries, including stabilization of a medially luxated patella (n=4), triple tibial tuberosity osteotomy for CCL tear (n=18), tibial wedge ostectomy for CCL tear (n=1), total hip replacement (n=13), external fixator placement for fracture repair (n=4), and removal of a fragmented medial coronoid process (n=1). Surgery types for the 36 dogs that completed the trial were subsequently grouped into "Hip" (n=11), "Knee" (n=21), and "Other" (n=4).

There were no significant group differences found between the hip and knee groups for dog age (Wilcoxon two-sample test, N_1=11, N_2=21, Z=−1.4659, p=0.1427) or dog weight (Wilcoxon two-sample test, N_1=11, N_2=21, Z=0.5754, p=0.5651). Due to the small number of dogs in the "Other" category, and the diversity of surgeries in that group, these dogs were excluded from the analysis of group differences by surgery type.

Trazodone Dosage and Schedule

After the post-surgical initiation dosage, the mean standard daily dosage at week 2 was 13.73 mg/kg/day (6.24 mg/lb/day), divided into twice daily doses (mean 6.86 mg/kg q 12 h; 3.12 mg/lb q 12h). At various times after week 2, 11 clients (29.7%) requested an increase in the dosage of trazodone for their dogs in order to improve confinement tolerance, and these dogs became the "high dosage" group. As increases in dosage may have taken place during different weeks after week 2, we defined the highest daily dosage each dog received during the study period as the "peak dosage." When increased, the mean peak dosage for these 11 dogs was 7.06 mg/kg [3.21 mg/lb], PO, q 8 h. Their mean total daily peak dosage was 21.19 ± 6.39 mg/kg/day [9.63 ± 2.90 mg/lb/day], PO, divided. The dogs in the "high dosage" group did not differ from those that received standard dosage on the basis of age (Wilcoxon two-sample test, N_1=25, N_2=11, Z=−0.5706, p=0.5682), or weight (Wilcoxon two-sample test, N_1=25, N_2=11, Z=−0.2919, p=0.770). When analyzed by surgery group ("Hip" vs. "Knee"), there was no difference between the surgery type for peak daily dosage given (Wilcoxon two-sample test, N_1=11, N_2=21, Z=0.0092, p=0.9216). There was also no difference in the distribution of dogs in the "high dosage" group vs. the "standard dosage" by surgery type (Fisher's exact test, p=0.7026).

Trazodone Onset of Action and Duration

As reported by clients, the median onset of action of trazodone was 31–45 minutes (Figure 1) and the median duration of action was four or more hours (Figure 2).

Behavioral Outcomes

The final survey responses compared to the pre-surgical survey responses revealed that dogs treated with trazodone significantly improved with respect to the intensity of greeting behavior to the client and to other familiar persons (Wilcoxon rank sum test, Z= −3.0026, P= 0.0027) and with respect to overall calmness (Wilcoxon rank sum test, Z= −1.8508, P=0.0321). Dogs treated with trazodone did not significantly improve with respect to willingness to be controlled by the client using familiar commands (Wilcoxon rank sum test, Z=−0.0197, P= 0.4921) and tendency to pull on leash walks (Wilcoxon rank sum test, Z= −1.2974, p = 0.0972). Dogs that received standard dosage or high dosage of trazodone did not differ in their pre-surgical rating of calmness (Fisher's Exact Test, table probability = 0.017; p = 0.6695) or in measures of confinement tolerance (Fisher's Exact Test, table probability = 0.0612; p = 0.4700).

Effect of Trazodone on Confinement Tolerance and Calming

In the final survey, 88.89% of all clients rated trazodone as moderately or extremely helpful for confinement tolerance (Figure 3). In contrast, at week 1, trazodone was evaluated as

moderately or extremely helpful for confinement tolerance by 58.33% of all clients (45.45% for dogs that subsequently received high dose trazodone). No clients rated trazodone as "not at all helpful" in facilitating confinement tolerance.

In the final survey, 88.89% of all clients rated trazodone as moderately or extremely helpful for calming (Figure 3). At week 1, trazodone was evaluated as moderately or extremely helpful for calmness by 61.11% of clients (45.45% for dogs that subsequently received high dose trazodone). At the final survey, trazodone was more likely to be reported as "extremely helpful" in dogs that initially resisted confinement compared to those which initially accepted confinement (Cochran-Mantel-Haenszel Test (CMH1 statistic = 6.536, df=1, p =0.011). At study completion, 25 of 36 dogs (69.4%) continued to receive trazodone per client request. Of these, four dogs (16%) received trazodone once daily, 16 dogs (64%) received trazodone twice daily, and 5 dogs (20%) received trazodone thrice daily.

Adverse Events

Clients were queried about adverse events in each weekly survey, and were able to respond in a free-text field. Over the course of the study, at least one adverse event which occurred at least one time was recorded for 20 patients (55.5%) (Table 1). No dog was withdrawn from the study due to an adverse event. No clients reported seizures, ongoing akathisia (state of motor restlessness), or priapism. No dogs presented with signs consistent with serotonin syndrome. Two incidents resulted in dogs accidently receiving higher dosages of trazodone than prescribed. One dog was accidentally given two dosages, receiving a total trazodone dosage of 600 mg (20 mg/kg [9 mg/lb], PO). He was evaluated by the NCSU-CVM Emergency Service and assessed as "slightly sleepy with normal vital signs and blood work" and recovered at home uneventfully. In another case, a client erroneously continued tramadol administration for more than 3 days, such that therapeutic dosages of tramadol and standard dosage (rather than initiation dosage) of trazodone were administered concurrently for two weeks; no adverse events were reported.

Concomitant Medications

During the study, dogs were administered concomitant medications as prescribed by their orthopedic surgeon or primary veterinarian. These medications, recorded by each client on the weekly survey, covered a wide range of medication classes (Table 2) and were administered at various doses and durations. No adverse events were reported by clients in response to concomitant medication administration.

Laboratory Values

Serum chemistry and complete blood count values before surgery and at the final visit (0–4 weeks after trazodone discontinuation) were independently evaluated by surgical clinicians and residents. The few values outside laboratory reference range were not considered clinically significant.

Discussion

In terms of efficacy, approximately 90% of clients reported moderate or extremely positive effects of their dogs' treatment with trazodone to facilitate post-surgical confinement tolerance and calming. Compared to pre-surgical baseline behavioral assessment, intensity of client greeting and overall calmness improved over the course of the study. There was no positive or negative effect of trazodone on the tendency of dogs to pull on leash walks and willingness to be controlled by the client using familiar commands, suggesting that it did not improve or inhibit trained responses.

In terms of safety, trazodone was well-tolerated at any dosage administered. There were no veterinary recommendations to discontinue trazodone during the study, and no client discontinued trazodone. During the study, there were no adverse effects that required medical treatment, dosage adjustment, or withdrawal of trazodone. The most common side effect of dogs that received trazodone was transient "drugged" affect, but no clients reported ataxia, disorientation, or stumbling. Thus, there appeared to be no motor impairment that might contribute to a fall during the surgery recovery phase. Other side effects were uncommon and manageable. One dog was accidently given 20 mg/kg/dosage of trazodone and suffered no adverse events per veterinary evaluation except sleepiness. Priapism (retained penile erection), a very rare side effect associated with trazodone use in human males, was not observed in any dog at any dosage. Transient anxiety/restlessness/agitation was reported by two clients as a single adverse event (Table 1). Because of their short duration, the reported behavior was not consistent with akathisia, an ongoing state of motor restlessness. Akathisia is a potential side effect of behavioral drugs, but not commonly reported as a consequence of the use of trazodone in humans.[6] In fact, trazodone has been reported to be therapeutic for the treatment of neuroleptic-induced akathisia.[19]

At the conclusion of the study, all dogs were physically examined by veterinary surgeons or surgical residents and no significant clinical abnormalities were observed. Although evaluation of post-study laboratory results revealed values outside laboratory reference range for some dogs, these were considered by clinicians to be benign and not significant. None required further evaluation. Trazodone was also safely administered with a range of concomitant medications including non-steroidal anti-inflammatories (NSAIDS) and antibiotics. In general, NSAIDS were administered for up to 7 days following surgery, and owners were asked to disclose medications that their dog received on each survey, however the possibility exists that owners administered individual doses of an NSAID without report. Due to the ability of NSAIDs to decrease pain, and therefore influence pain-related behavior, this is a potential confounding factor in the study.

Because of concerns that concurrent use of two serotonergic agents, tramadol and trazodone, might produce an excess of serotonin, trazodone was administered at a sub-therapeutic initiation half-dosage until tramadol use was discontinued. Tramadol, a centrally acting synthetic analgesic, is in the opioid class of drugs. Its action may inhibit the reuptake of serotonin,[20] potentially leading to a toxic concentration of serotonin in the central nervous system, a condition called serotonin syndrome. Signs of serotonin syndrome may include neurological signs of disorientation/confusion, motor restlessness, hyperreflexia, myoclonus,

tremor, seizures; gastrointestinal signs including vomiting and diarrhea, and signs of physiological decompensation such as hyperthermia.[17,21] In the present study, no dogs exhibited any signs consistent with serotonin syndrome. One client, in error, administered to her dog the standard dosage of trazodone in combination with tramadol for 1 week without negative effect.

Most clients reported that trazodone acted promptly, with the median onset of action of oral administration within 31–45 minutes. By client report, the duration of action of trazodone was 4 or more hours. In humans, oral trazodone undergoes a biphasic elimination pattern with a fast phase of 3–5 hours followed by a slower phase lasting 6–9 hours.[8] A pharmacokinetic study of single-dose oral trazodone in dogs revealed an elimination half-life of 166 ± 47 minutes.[13] In the present study, cases in which the duration of action seemed insufficient, on an individual basis the trazodone dose schedule was increased to three times daily.

Peak daily dosages given to dogs in the present study ranged from 8.0 mg/kg/day (3.6 mg/lb/day) to 30.9 mg/kg/day (14.0 mg/lb/day); all dosages were divided into two or three times per day. Dogs, as humans, appear to have a wide effective and safe dosage range of trazodone.

In general, clients were gratified by the positive effect of trazodone on their dogs, and commented favorably in the free text portion of the survey on the effectiveness of trazodone as an aid to necessary post-surgical confinement. In spite of the necessity of administering oral medication to their dogs daily, the majority of clients (69%) elected to continue use of trazodone after the first four weeks. The current open trial did not allow evaluation of the placebo effect known to be present in human and veterinary studies.[22,23] Positive findings could be due to a conditioned (learned) response of the dog to confinement over time, response to behavioral therapy administered by the client, positive client expectation following specialty surgery. It is also possible that owners could misinterpret pain in their dog as calmness, though the ability of trazodone to facilitate behavioral calming and confinement at times distant from the surgery, and administration of pain medications during the early post-operative period decrease this as a potential mitigator. In addition, many clients had noted pain in their dogs as a presenting concern for orthopedic evaluation, and so were likely able to distinguish pain from the effects of the trazodone. A future randomized, double-blinded, placebo-controlled study will more fully evaluate the critically important placebo effect.

In summary, the behavioral drug trazodone, at a wide dose range, appeared to be a safe and useful modulator of behavior. Administration of trazodone facilitated recommended confinement and calming required during the 8–12 weeks following elective orthopedic surgery, performed at a veterinary referral hospital. Pre-surgical behavioral evaluation of “calmness” and “tolerance of confinement” did not predict the final dose of trazodone given.

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Abreviations

LD_{50}	Median lethal dosage
PO	*per os*

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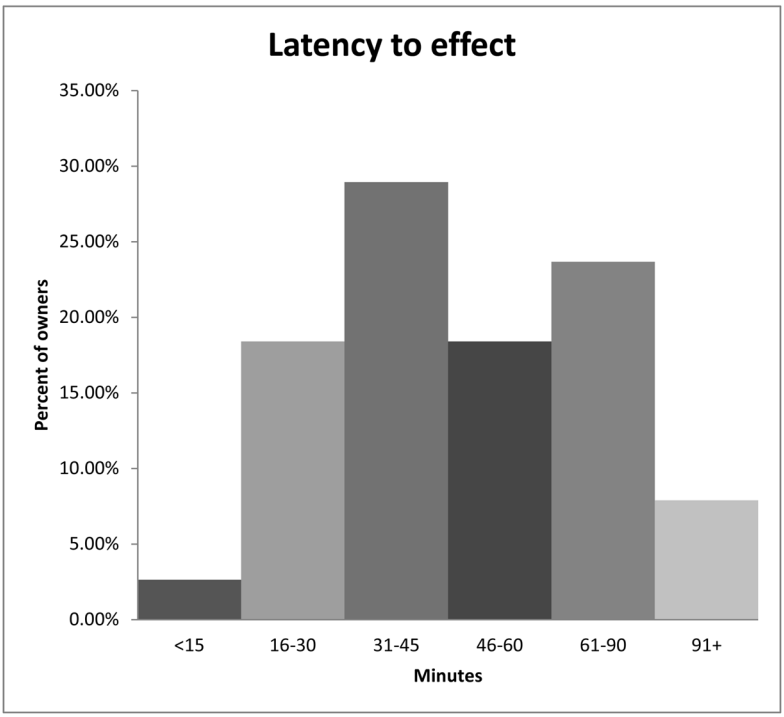

Figure 1.

Latency to trazodone effect per client report at the final survey. The greatest percent of clients reported the effect of trazodone was observed within 31–45 minutes of administration. Over 90% percent of clients reported latency of effect between 16–90 minutes.

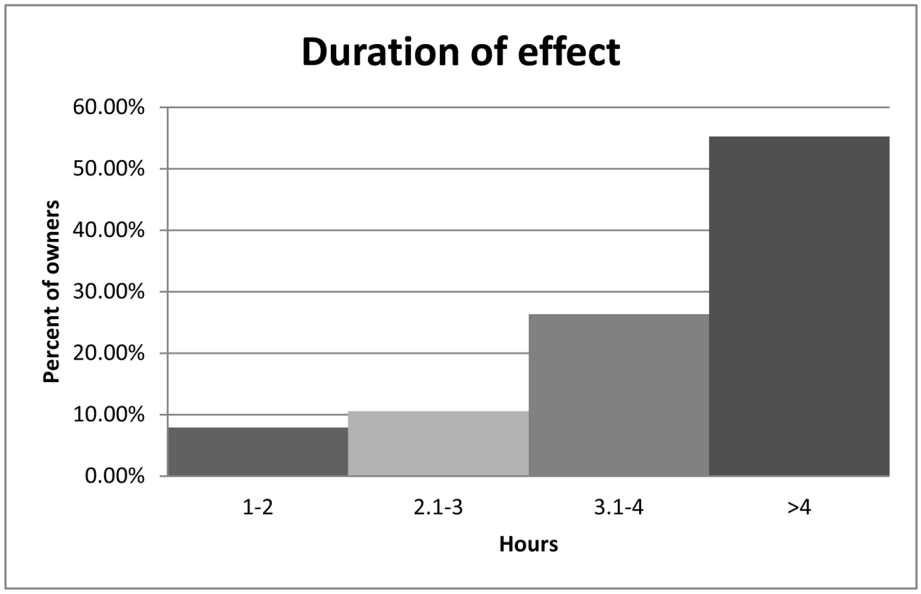

Figure 2.

Duration of trazodone effect per client report at the final survey. The majority of clients reported duration of behavioral effect of trazodone to be 4 or more hours.

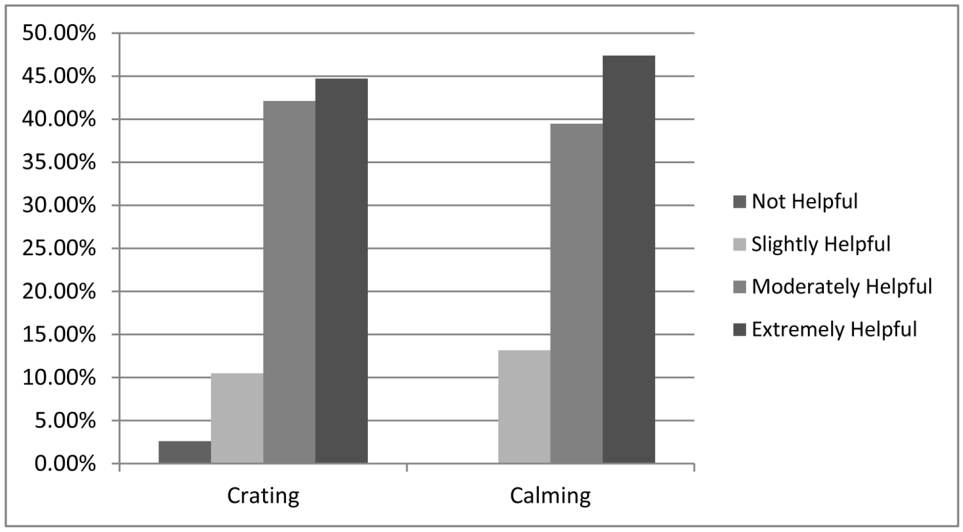

Figure 3.

Client's evaluation of the helpfulness of trazodone treatment on confinement tolerance and calming at the final survey. Percent of owners providing each response is shown.

Table 1

Adverse events: Over the course of the study, at least one adverse event which occurred at least one time was recorded for 20 of 36 patients that completed the trial (55.5%). These may have been listed on only one or on repeated surveys. No dogs were removed from the trial due to adverse events.

Adverse event/sign	Number of dogs with event/sign reported	Percentage of dogs with event/sign reported
Gastrointestinal		
Soft stool, loose stool, diarrhea	1	2.7
Constipation	1	2.7
Increased thirst	1	2.7
Behavioral		
Anxiety/restlessness/agitation	2	5.4
Aggression*	1	2.7
Moaning	1	2.7
Drowsy	2	5.4
Drugged/spacey*	5	13.5
Other		
Panting	2	5.4
Teeth chattering*	1	2.7
Drooling	1	2.7
Paranoid	1	2.7
Leaking urine	1	2.7

* One unexplained case of aggression/drugged/teeth chattering was associated with single administration of a 300 mg generic trazodone tablet obtained by the client from a local pharmacy. These signs did not re-appear when the prescription was filled for the same dose (300 mg) using three 100 mg tablets from NCSU pharmacy.

Table 2

Concomitant medications by class: Medications administered to dogs during the course of the study and the number of dogs receiving at least one drug in each class. Because of their special interest, non-NSAID pain medications are listed by drug. Unless otherwise noted, medications were administered *per os*. The list of drugs was compiled from client surveys at initial enrollment and during the course of the study (n=41).

Drug class	Specific Agents Given	Number of dogs
Antihistamines	Diphenhydramine, hydroxazine	4
Behavioral medications	Fluoxetine,* acepromazine	3
Flea prophylaxis	Fipronil, Imidacloprid	12
GIT medications	Probiotic	1
Heartworm prophylaxis	Ivermectin, selamectin, milbemycin	14
Non-steroidal anti-inflammatories (NSAID)	Carprofen, deracoxib, tepoxalin, firocoxib, or meloxicam	41
Nutraceuticals	Glucosamine/chondroitin, fish oil	26
Other pain medications (non-NSAID)	Tramadol	38
	Gabapentin	2
	Amantadine	1
Steroids	Prednisone	1
Systemic antibiotics	Cephalexin, cefpodoxime, amoxicillin, amoxicillin/clavulanic acid, clindamycin, rifampin, marbofloxacin, metronidazole	20
Topical Treatments	Triple antibiotic ointment, chlorhexadine, chlorhexadine/ketoconazole	8

* The dog receiving fluoxetine was withdrawn from the study due to exclusion criteria violation