

Use of trazodone as an adjunctive agent in the treatment of canine anxiety disorders: 56 cases (1995–2007)

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Objective—To evaluate efficacy of trazodone hydrochloride as an adjunctive treatment for anxiety disorders as well as treatment protocol, dose range, concurrent drug use, adverse events, and therapeutic response in dogs unresponsive to other pharmacologic agents.

Design—Retrospective case series.

Animals—56 dogs with anxiety disorders treated at a referral veterinary behavior clinic.

Procedures—Medical records of dogs with anxiety disorders adjunctively treated with trazodone were retrospectively evaluated with respect to signalment, primary and secondary behavioral diagnoses, physical examination results, hematologic data (CBC and serum biochemical panel), pharmacologic management, and outcome.

Results—Overall, trazodone, used as an adjunctive agent in combination with other behavioral drugs, was well tolerated over a wide dose range and enhanced behavioral calming when administered on a daily or as-needed basis.

Conclusions and Clinical Relevance—Although further controlled studies of dose range, efficacy, and safety are needed, trazodone may provide an additional therapeutic option for use in dogs that are unresponsive to conventional treatment. (*J Am Vet Med Assoc* 2008;233:1902–1907)

Anxiety disorders, fears, and phobias are among the most common behavioral problems of companion dogs.¹ These problems include generalized anxiety, separation anxiety, and phobias of specific stimuli such as storms, fireworks, or other noises. In each of these disorders, affected dogs exist in a state of heightened arousal and distress. They may cause damage to their surroundings or themselves as an expression of their anxiety. As such, anxiety disorders represent an important welfare issue for affected dogs and may negatively impact the human-animal bond. Results of a previous study² indicate that destructive behaviors, as often observed in dogs with separation anxiety, are a major reason why dogs are relinquished to animal shelters.

Treatment of anxiety disorders is often challenging and time-consuming, involving a combination of behavioral management and anxiolytic medication. A number of psychoactive medications have been used for treatment of canine anxieties, fears, and phobias, including TCAs, SSRIs, benzodiazepines, and the azapirone agent buspirone,³ with various degrees of treatment success.

Several double-blind, placebo-controlled clinical trials^{4,5} revealed improvement in dogs treated with a single pharmacologic agent in combination with behavioral management for short-term treatment of separation anxiety. In a multicenter study⁴ of clomipramine for treatment of separation anxiety, 73% of the dogs treated with a combination of the drug and behavior modification were described as much improved or cured

ABBREVIATIONS

CYP	Cytochrome P450
SARI	Serotonin 2A antagonist/reuptake inhibitor
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant

by their owners after 12 weeks of treatment, compared with 41% of dogs in the placebo group (behavior modification only). The improvement in the clomipramine-treated group was significantly greater than that of the placebo control group.⁴ A separate multicenter study⁵ of fluoxetine for treatment of separation anxiety found that, after 8 weeks of treatment, 72% of dogs receiving fluoxetine in conjunction with behavior modification had improvement of clinical signs, compared with placebo in conjunction with behavior modification; the difference was significant. Although both studies revealed significant improvement with single-agent therapy and behavioral management, approximately 30% of dogs did not respond satisfactorily.

An adjunctive agent is needed to enhance pharmacologic treatment of dogs with anxiety disorders insufficiently responsive to conventional treatment protocols as well as dogs initially responsive to treatment that relapse over time. Complicated cases and dogs with more than 1 behavioral diagnosis may also benefit from this approach. In addition, an agent that can be administered effectively on an as-needed basis would be useful for sporadic problems, such as storm phobia.

When a primary agent is inadequate and a behavioral plan has been implemented, the addition of a second psychotropic agent may increase efficacy and decrease

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adverse effects.⁶ In human psychiatric medicine, it is common to combine drugs to improve response to treatment.⁷ This practice is increasingly widespread among veterinary behaviorists faced with cases in which treatment with a single agent provides inadequate response.^{6,8,9}

Selection of an appropriate adjunctive agent may be limited by the patient's health status and clinical signs. Benzodiazepines, frequently used as adjunctive treatments, may not be sufficiently effective or may be inappropriate for certain animals because of behavioral adverse effects, such as behavioral disinhibition of aggression, increased appetite, or paradoxical excitatory reactions.^{3,10} These and other cases require an alternative agent to augment the behavior management and enhance behavioral calming. In our clinic, the atypical antidepressant trazodone hydrochloride has been used as an effective adjunctive agent to fill this niche.¹¹

First synthesized in Italy in 1966, trazodone has been used for many years in human patients as a well-tolerated antidepressant,^{12,13} antiobsessional agent,¹⁴ and anxiolytic.¹⁵ It may be less effective than other agents in the treatment of acute panic disorder.¹⁶ When used in combination with an SSRI or TCA, trazodone may be synergistic.^{7,17,18} One study¹⁹ found that when a subtherapeutic dose of trazodone was combined with a low dose of fluoxetine, 75% of depressed patients treated had a clinically relevant response, compared with 20% of those that received trazodone alone. Presently, the most common indication for trazodone is as an effective adjunctive treatment to reduce anxiety and facilitate sleep in depressed or anxious patients receiving TCAs or SSRIs.²⁰⁻²³

Trazodone hydrochloride is a triazolopyridine derivative and member of the phenylpiperazine class of drugs. It is classified as a SARI on the basis of its primary pharmacologic mechanism of action to antagonize serotonin 2A receptors and its secondary mechanism to inhibit serotonin reuptake.¹⁷ Trazodone and its active metabolite, *m*-chlorophenylpiperazine (*m*-CPP), also have agonistic effects at serotonin 1 receptors.²⁴ Recent evidence suggests that trazodone may also increase serotonin concentrations by attenuating the inhibitory tone of γ -aminobutyric acid neurotransmitters in the cerebral cortex, suggesting that its mechanism of action as an antidepressant and anti-anxiety agent is distinct from that of the SSRIs, TCAs, and benzodiazepines.²⁵

In humans, evaluation of trazodone pharmacokinetics reveals that it is extensively metabolized, with < 1% being excreted unchanged in the urine. The most important metabolite of trazodone, *m*-CPP, is generated by CYP3A4 metabolism and is broken down by CYP2D6. This metabolite, which is also active at serotonin 2C receptors, may account for the uncommon adverse effects such as nausea and headache²⁶ that occasionally develop following trazodone administration.²⁷ Trazodone absorption is more rapid in fasted subjects, with peak blood concentrations occurring approximately 1 hour after administration versus 2 hours when taken with food.²⁸ However, the plasma concentration-time curve is increased when trazodone is taken with a meal.²⁹ Trazodone then undergoes a biphasic elimination pattern with a fast phase of 3 to 5 hours followed by a slower phase lasting 6 to 9 hours.

Trazodone has a low frequency of serious adverse effects in humans and is prescribed over a wide dose range, from 150 to 600 mg/d.²⁹ In humans, trazodone induces fewer anticholinergic signs than the tricyclic antidepressants.²⁹ In anesthetized dogs, trazodone has little effect on cardiac function, compared with equally effective doses of imipramine.³⁰ In human clinical trials, no seizures were observed,³¹ and trazodone has been listed among the antidepressants with the lowest seizure risk.³²

Although trazodone has an extensive history of use in humans, little clinical data are available on the use of this drug in dogs.^{3,8,11} The objectives of the present study were to evaluate use of trazodone hydrochloride as an adjunctive treatment for anxiety disorders in dogs unresponsive to other pharmacologic agents as well as evaluate treatment protocol, dose range, concurrent drug use, adverse events, and therapeutic response during 12 years of use in a clinical outpatient behavior practice.

Materials and Methods

Case selection—The study included 56 privately owned dogs referred to a veterinary behavior clinic and subsequently treated with trazodone between 1995 and 2007. Dogs were included in the study if they had been given a primary or secondary diagnosis of an anxiety or phobic disorder, had been treated with trazodone, and had subsequent follow-up for at least 1 month. Anxiety or phobic disorders included generalized anxiety, separation anxiety, travel anxiety, storm phobia, noise phobia, and combinations thereof. For all dogs, a detailed customized behavior management was provided to the client in writing at the initial consultation. Dogs prescribed trazodone for treatment of non-anxiety disorders were excluded from this study.

Medical records review—Information extracted from the medical records included sex, breed, weight (kg), age at referral, and primary and secondary behavioral diagnoses. Information specific to trazodone included protocol for initiation, concomitant drug administration, administration schedule (daily, as needed, or both), initial and final dosage (mg/kg and mg/lb), reported adverse events, clients' assessment of therapeutic effect, duration of use, physical evaluation, and laboratory values (CBC and serum biochemical panel). Subjective evaluation of satisfactory therapeutic response was made by use of client report in the record, continuation of administration for at least 3 months, or both.

All dogs were treated with individually tailored behavior management programs at the same veterinary referral behavioral practice in conjunction with medication. The general pharmacologic treatment protocol was as follows: a baseline dose of a TCA (clomipramine, amitriptyline, or imipramine) or an SSRI (fluoxetine, sertraline, or citalopram) was established by use of published^{3-5,10} and empiric guidelines. Over time, if these agents proved insufficient to provide adequate relief of clinical signs of anxiety, even with dose and administration schedule adjustments, administration of trazodone was added. The duration of the period before administration of trazodone

after the initial consultation ranged widely from 0 to 228 weeks (mean, 21 weeks). Dogs for which trazodone administration was begun at week 0 generally had a previous prescription for a baseline medication at an adequate dose. The decision to begin trazodone administration was based on the joint assessment of the clinician and client. Trazodone administration was begun at an initiation dose (half of the initial target dose administered for 3 days) to permit dogs to become tolerant to the drug and avoid potential gastrointestinal adverse effects. This strategy was implemented because, in a preliminary trial, a small percentage of dogs that initially received the full target dose developed sedation or adverse effects (transient soft feces or diarrhea) presumptively attributed to trazodone. After the initiation dose, the target dose was established as the lowest effective dose needed for behavioral calming. Additional dose increments were made empirically over time. All clients were warned not to concurrently administer monoamine oxidase inhibitors, including amitraz products. The health status of all dogs that continued to receive trazodone was evaluated annually by use of physical examination, CBC, and serum biochemical panel.

Statistical analysis—Descriptive statistics and *t* tests were performed on breed, age, weight, and dosage data with a commercially available statistical software package.^a A *P* value < 0.05 was considered significant.

Results

Cases—Dogs meeting study criteria included 26 spayed females, 29 neutered males, and 1 sexually intact male that was neutered according to plan during the course of treatment. Thirty-eight (67%) dogs represented 18 distinct recognized breeds, whereas the remaining (33%) dogs were of mixed breed. Weights ranged from 5.2 to 45.5 kg (11.4 to 100.1 lb), with a mean of 27.3 kg (60.1 lb). Ages at referral ranged from 11 to 156 months, with a median of 54 months. All dogs were medically screened via physical examination, CBC, serum biochemical profile, and thyroid panel prior to pharmacotherapy. All dogs had follow-up for at least 1 month following initiation of trazodone administration. Thirty-seven (66%) dogs had follow-up for at least 1 year following initiation of trazodone treatment. Of the remaining 19 dogs, 3 were in their first year of trazodone treatment at the time of the study, 12 were lost to follow-up prior to 1 year of treatment, and 4 received trazodone for < 1 year. Those 4 dogs included 3 in which trazodone administration was discontinued because of adverse effects and 1 that was euthanized for unrelated health reasons.

There was a range of diagnoses. Separation anxiety and storm phobia were the most common diagnoses, each occurring in 27 dogs. Other anxiety-related diagnoses included generalized anxiety (*n* = 13), noise phobia (8), canine compulsive disorder (3), travel phobia (2), and inoculation phobia (1). Thirteen dogs had aggression as either a primary or secondary diagnosis; however, each of those dogs had a concurrent anxiety disorder. Total number of diagnoses exceeded the number of dogs because each dog could have up to 2 diagnoses.

Concomitant psychoactive medications included TCAs (clomipramine, amitriptyline, and imipramine)

in 31 dogs, SSRIs (fluoxetine, sertraline, and citalopram) in 21 dogs, benzodiazepines (alprazolam, lorazepam, and clorazepate) in 18 dogs, the azaspirone buspirone in 12 dogs, the antipsychotic reserpine in 2 dogs, and a nutraceutical (melatonin) in 1 dog. Twenty-one dogs received more than 2 psychoactive medications concomitantly, including 12 dogs treated with an SSRI or TCA in combination with a benzodiazepine. Concurrent nonpsychoactive medications prescribed by the referring veterinarian included antimicrobials, heartworm preventative products (oral and topical administration), flea preventative products, antihistamines, nonsteroidal anti-inflammatory medication, and thyroid hormone supplementation. No amitraz products were coadministered. One dog was also receiving potassium bromide for seizures that existed prior to trazodone administration. Several dogs were anesthetized without complications for elective surgeries during their course of trazodone treatment.

Irrespective of administration schedule, all dogs initially received trazodone at a low initiation dose, then received an increased preliminary target dose and, if needed, then received an empirically titrated higher dose over weeks or months to achieve behavioral calming. The initiation and preliminary target doses were chosen on the basis of weight (Table 1). The number of dose adjustments made varied by individual, severity of clinical signs, and duration of trazodone administration. Three administration schedules were used in combination with an SSRI or TCA: 14 dogs received trazodone as a daily medication, 20 received trazodone as needed for anxiety, and 22 received trazodone both daily and as needed. Choice of administration schedule was empiric and depended on the judgment of the clinician. In general, dogs with generalized forms of anxiety disorders were treated daily with trazodone, whereas dogs with anxiety that appeared more episodic or had recognized triggers, such as storm phobia, were treated as needed. Seven dogs with storm phobia received daily and as-needed administration during the storm season (April through September). Minimum and maximum dosages prescribed and mean daily dosage for each administration were tabulated (Table 2). The high-

Table 1—Initiation and target dosages of trazodone in dogs of various weight classes.

Weight	Initiation dosage range	Target dosage range
< 10 kg	≤ 25 mg, q 8–24 h	≤ 50 mg, q 8 h–24 h
≥ 10–20 kg	50 mg, q 12–24 h	100 mg, q 8–24 h
≥ 20–40 kg	100 mg, q 12–24 h	200 mg, q 8–24 h
> 40 kg	100 mg, q 12–24 h	200–300 mg, q 8–24 h

To convert kilograms to pounds, multiply by 2.2.

Table 2—Minimum, maximum, and mean daily trazodone dosages by administration schedule in 56 dogs.

Administration schedule	Minimum	Maximum	Mean
Daily medication only	1.9 mg/kg/d	16.2 mg/kg/d	7.3 mg/kg/d
As needed only	2.2 mg/kg/d	14 mg/kg/d	7.6 mg/kg/d
Daily medication and as needed	1.7 mg/kg/d	19.5 mg/kg/d	7.25 mg/kg/d

To convert mg/kg/d to mg/lb/d, divide by 2.2.

est dosage (19.5 mg/kg [8.86 mg/lb]) represented dogs in which trazodone was given both daily and as needed (at the maximum dose allowed as needed).

By use of a paired *t* test, no significant relationship between body weight and dosage was found. Mean maximum trazodone dosages for 4 weight classes were calculated (Table 3).

No dog received an individual dose of trazodone > 300 mg. The maximum daily dose was 600 mg, which represented a combined twice-daily and as-needed dose in a dog that weighed 36 kg (79.2 lb). For as-needed doses, most clients observed that behavioral effects occurred within 1 to 2 hours of trazodone administration.

Among the 56 dogs, reported adverse events included vomiting (*n* = 1), gagging (1), colitis (1), increased excitement (2), sedation (2), increased appetite (2), and perceived behavioral disinhibition (2). Behavioral disinhibition consisted of getting onto counters (*n* = 1) and opening the trash can (1) in dogs that had not previously had these behaviors. Except for 1 case of colitis (reported 1 month after initiating treatment with trazodone), soft feces and diarrhea were not reported during treatment at any dose. In 3 dogs, trazodone administration was discontinued because of adverse effects attributed to the medication. One of the dogs was described as gagging when given trazodone, 1 had behavioral disinhibition (getting onto counters), and the third developed colitis. No relationship was found between breed, age, baseline medication, administration schedule, or trazodone dose and risk of adverse events.

Outcome—Each dog was evaluated during at least 1 follow-up appointment after initiation of trazodone administration. Client reports of therapeutic efficacy, continuation of trazodone administration for at least 3 months after initial prescription, or both were used as an indication of satisfactory response. Most clients for whom a direct comment was recorded in the clinical record (*n* = 40) stated that their dog was either very (29 [72.5%]) or somewhat (5 [12.5%]) improved as a result of use of trazodone as an adjunctive agent. Three (7.5%) clients reported no effect of trazodone on their dog's anxiety, and 3 (7.5%) reported adverse effects that led to discontinuation of treatment, as described. For 16 (28.6%) dogs, no direct comment was made in the record regarding the specific effect of the medication.

Using continuation of treatment for > 3 months as a measure of treatment satisfaction, trazodone administration was useful in the treatment of anxiety for 46 (82.1%) dogs. Duration of treatment with trazodone

for those dogs ranged from 3 to 95 months (almost 8 years), with a mean of 24.8 months.

Each of the 3 dogs for which clients reported no effect of trazodone administration for anxiety had been previously resistant to other behavioral medications and behavioral management. One was a Golden Retriever with storm phobia being treated with fluoxetine, alprazolam, hydroxyzine, and trazodone. The others were Pit Bull Terriers, one with a diagnosis of separation anxiety and one with a diagnosis of separation anxiety and generalized anxiety. One of these was treated with fluoxetine, alprazolam, and trazodone. The other was treated with clomipramine, alprazolam, and trazodone.

All dogs for which treatment continued past 1 year received medical screening annually. There were no clinically relevant abnormalities in laboratory values over time for dogs included in this study.

Discussion

Results indicated that trazodone was useful and tolerated over a wide dose range in dogs, in combination with behavioral management and drugs from the TCA, SSRI, benzodiazepine, and azaspironone classes. In addition to psychoactive medications, all dogs included in the study concurrently received routine flea, tick, and heartworm preventative medications, with no adverse events detected when administered. During the study, several dogs received antihistamines, NSAIDs, antimicrobials, or anesthetic drugs for elective surgery with no reported complications. No dogs received monoamine oxidase inhibitors or amitraz-containing products during the course of the study.

Starting trazodone treatment at a low initiation dose and increasing the dose over time was used strategically to reduce the probability of adverse effects and monitor the dog's progress. Trazodone targets serotonin receptors located primarily in the CNS; however, effects on the receptor subtypes serotonin 3 and serotonin 4 located in the gastrointestinal tract³³ are possible.³⁴ Gradually increasing the dose of trazodone may have reduced the potential for gastrointestinal adverse effects.

Because trazodone affects central serotonin receptors and is commonly prescribed in combination with other serotonergic agents, concerns may arise regarding the risk of serotonin syndrome or toxicoses in humans³⁵ as well as dogs. Trazodone is extensively prescribed in humans in combination with SSRIs and TCAs; reports of serotonin toxicosis are limited to individual case reports of coadministration of trazodone with fluoxetine,³⁶ risperidone-sertraline,³⁷ amitriptyline-lithium,³⁸ and venlafaxine.³⁹ No dogs in the present study had signs consistent with serotonin toxicosis such as hyperthermia, tremor, or seizures. All concurrently prescribed serotonergic drugs were used at published or accepted empiric doses. For example, no dog receiving trazodone received fluoxetine at higher than the approved 1 to 2 mg/kg/d (0.45 to 0.91 mg/lb/d) dosage.⁵ However, serotonin toxicosis is a potential adverse event and should remain on the differential list for any dog with clinical signs consistent with this diagnosis. In cases of suspected serotonin toxicosis, supportive care

Table 3—Mean maximum trazodone dosages in dogs of various body weights.

Weight	Mean maximum dosage	No. of dogs
≤ 10 kg	11.70 mg/kg/d	2
≥ 10–20 kg	9.91 mg/kg/d	7
≥ 20–40 kg	8.87 mg/kg/d	43
> 40 kg	5.40 mg/kg/d	4
See Table 2 for key.		

should be provided immediately; there is no specific antidote for trazodone.

Priapism (prolonged penile erection) is a rare but important adverse effect, reported in postmarketing studies of trazodone in < 1% of humans treated.⁴⁰ Estimates of trazodone-induced priapism are between 1/6,000 and 1/10,000 persons treated.⁴¹ The mechanism for priapism is not known, but it is speculated to involve the interplay of diverse neuroeffectors, hormones, vasoactive substances such as nitric oxide, signal transduction systems, and corporeal tissue, cellular, and molecular factors.⁴² Although it is not known whether this adverse effect occurs in dogs, as a cautionary measure, in our clinic, breeding males were not given trazodone. One sexually intact, nonbreeding male dog in this study received trazodone as part of a desensitization protocol in which entry to the veterinary clinic for castration was the desired outcome; no priapism was evident. In fact, no occurrence of priapism was observed in any dog to which trazodone was prescribed at any dose reported here.

In general, adverse effects with trazodone were mild, with only 3 dogs requiring discontinuation of the drug. In approximately 80% of dogs, no adverse effects were reported, despite the wide dose range used and duration of administration of trazodone. For most dogs, trazodone was well tolerated, with 77% of dogs receiving trazodone for > 3 months and many for multiple years.

The wide dose range used in these dogs was similar to the wide dose range in humans. As is common in humans, we used a low initial dose and titrated to effect over time. In humans, a dose range of 150 mg/d to 600 mg/d is frequently used.²⁹ Although the toxic dose of trazodone is not available for dogs, reported LD₅₀ doses in mice, rats, and rabbits are 610 mg/kg (277.3 mg/lb), 486 mg/kg (220.9 mg/lb), and 560 mg/kg (254.5 mg/lb), respectively, indicating a large margin of safety in these mammals.³¹

In the present study, trazodone was not used as a treatment for aggression. However, several dogs included in the study had some aggression as part of their spectrum of signs. No increase of aggression was reported in those dogs. Similarly, aggression was not reported as an adverse event in any dog. Behavioral disinhibition is often cited as a cause for the increase in aggression that may be seen when aggressive dogs are given benzodiazepines.³ Although increased aggression was not observed in any of the study dogs, 2 dogs had apparent behavioral disinhibition manifested as the forgetting of a learned behavior. This may also have been the result of increased hunger which, although not reported in humans, was reported in 2 dogs in the present study. Also, it is possible that the disinhibition was related to an increase in anxiety or dysphoria, which would need to be investigated in future studies with this drug. In humans, cognitive function, assessed by tests of immediate and short-term memory, was unaffected by administration of trazodone up to 400 mg/d.⁴³

In most dogs in the present study, trazodone was prescribed as a result of the failure of or insufficient response to a comprehensive behavioral treatment plan coupled with conventional anxiolytic medications, in-

cluding combination treatment. On the basis of the severity of their clinical signs and their lack of response to conventional treatment, many of these dogs were at risk for relinquishment or euthanasia.

For all dogs in our study, the starting dose of trazodone was low and was titrated to effect. Over time, many dogs developed some tolerance to the drug, and the dose was increased empirically. Some dogs were given trazodone once or twice daily; others were administered the drug only when needed, as at the first sign of storm phobia.

Given the bias in the present study toward dogs that were nonresponsive to other treatments, the client-reported improvements were even more striking. Most dogs were reported to have relief of some or all signs of anxiety as a result of trazodone administration. For those dogs in which no specific response to trazodone was clearly noted in the record, most clients elected to continue trazodone treatment, many for several years, which suggested favorable client assessment. In each of the 3 dogs in which clients reported no anxiolytic effect of trazodone, multiple drugs and behavior modification techniques had been used without mitigation of clinical signs. One of the dogs was eventually euthanatized as a result of unrelenting signs, and 2 others were managed with a combination of medications.

Results of this retrospective case series suggested that in clinical behavioral practice, the SARI trazodone hydrochloride is a well-tolerated and useful medication for adjunctive treatment of canine anxiety disorders. Further controlled studies are needed to more fully evaluate the pharmacokinetics, safety profile, and efficacy of this drug in dogs.

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