Effects of trazodone administration on the neurologic examination in healthy dogs

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Abstract

Background: Trazodone is an anxiolytic used PO to decrease anxiety in dogs. Whether or not trazodone affects the neurologic examination in dogs has not been previously reported.

Objective: Investigate whether trazodone administration is associated with changes in the neurologic examination in healthy dogs.

Animals: Thirty-two healthy dogs between 1 and 6 years old with no previously diagnosed medical conditions and perceived by their owners as neurologically normal.

Methods: Baseline sedation and anxiety assessments and neurologic examination were performed on each dog, followed by trazodone administration (6.25-8.60 mg/kg PO). The sedation and anxiety assessments and neurologic examination were repeated 2.5 hours after trazodone administration. The examinations were performed by a single board-certified veterinary neurologist and were video-recorded. The videos were randomized and reviewed by a different neurologist, blinded to the previous evaluations, who scored the examinations.

Results: Seven of 32 (22%) dogs had worse scores on their neurologic examination after receiving trazodone, manifesting as new or progressive PR deficits. Although not clinically relevant, 18.7% of the dogs had consciousness levels that changed from bright, alert, responsive to quiet, alert, responsive after trazodone administration. No other changes were observed on neurologic examination. Sedation and anxiety scores were significantly different after trazodone administration compared to before (P < .001 and P < .001, respectively).

Conclusions and Clinical Importance: Most dogs did not have changes on neurologic examination after trazodone administration. However, approximately 20% of dogs had new or worsening PR deficits after receiving trazodone. Ideally, trazodone should not be given before neurologic examination in dogs.

Keywords: anxiety, canine, neurolocalization, neurology, sedation
1 | INTRODUCTION

A precise neurological examination is a crucial step in the diagnostic approach to patients with neurological problems. Accurate neurolocalization is essential for the development of a list of differential diagnoses, as well as for determining the correct area of the nervous system to be evaluated by further diagnostic testing. Abnormalities, or deficits, identified by the neurologic examination are used to determine if a patient has neurologic disease and, if present, to accurately localize the lesion.

For many dogs, the veterinary hospital setting induces stress and anxiety,\(^1,2\) which can increase the risk of infection\(^3-5\) and prolong wound healing.\(^6\) To mitigate these adverse reactions and minimize patient distress, PO anxiolytics and sedatives are increasingly used in dogs during veterinary visits or hospitalizations.\(^7,8\)

Although numerous pharmaceutical agents used as anxiolytics have the potential to induce sedation, trazodone is an attractive initial agent because of its wide safety margin, low risk of adverse effects, and length of activity.\(^9,10\) Trazodone is a PO anxiolytic frequently prescribed by veterinarians to decrease situational anxiety in dogs\(^7\) and can be administered in-hospital as well as at home, with increasing usage before examinations with the advent of fear-free practice. Trazodone is classified as a serotonin 2A antagonist and receptor inhibitor (SARI) and functions by potentiating the activity of serotonin within the synapse by preventing its reuptake.\(^12\)

In previous studies, trazodone administration resulted in fewer anxious behaviors and signs of distress in hospitalized dogs\(^10\) and decreased the level of anxiety in dogs diagnosed with anxiety disorders.\(^9\) Sedation after trazodone administration in dogs has been shown as a consistent adverse effect of the medication when administered PO.\(^9,13\)

The central nervous system is the target organ for anxiolytic medications.\(^14,15\) but it is not currently known how the neurologic examination is affected by this class of medications and, if so, to what extent. To our knowledge, no previous studies have been published that evaluate the effects of trazodone on the neurologic examination in dogs. Therefore, our purpose was to investigate whether trazodone causes detectable changes in the neurologic examination in dogs considered neurologically normal by their owners. We hypothesized that trazodone administration would lead to a change (decrease) in the level of consciousness as well as mild changes in gait and proprioceptive deficits of the limbs.

2 | MATERIALS AND METHODS

Our study used a prospective, masked, clinical cross-over design. The protocol was approved by the Institutional Animal Care and Use Committee at the University of Wisconsin - Madison, School of Veterinary Medicine. Written informed consent was obtained from the dog owners before enrollment in the study.

2.1 | Animals

Dogs owned by veterinarians, veterinary technicians, assistants, and veterinary students were recruited for the study. Dogs were eligible for enrollment if they met the following inclusion criteria: (a) were between the ages of 1 and 6 years, (b) had never been diagnosed with a chronic medical condition, (c) were perceived to be healthy and neurologically normal by their owners, and (d) were not receiving any medications. No laboratory diagnostic testing was required for participation. Dogs were excluded from the study if they were aggressive or resistant to restraint.

2.2 | Study design

Before each comprehensive neurologic examination, the levels of anxiety and sedation of all dogs were assessed. This process was utilized for both the pre- and post-trazodone assessments. The Grit Sedation Scale\(^16\) (as previously validated\(^17\)) and the Lincoln Canine Anxiety Scale (as previously validated\(^18\)) were used for sedation and anxiety assessment, respectively. Immediately after these assessments, each dog was given a single standardized dose of trazodone (between 6.25 and 8.60 mg/kg) PO. Dogs were not fasted before presentation. Within 105 to 195 minutes after administration of trazodone, anxiety and sedation scales and neurologic examinations were repeated. All anxiety and sedation scoring was performed by the same clinician (LL), and all neurologic examinations were performed by the same single board-certified veterinary neurologist (SC). All neurologic examinations, pre- and post-trazodone administration, were recorded by video by the same investigator (LL) using a standard iPhone 11 video camera. The scores from each dog’s pre- and post-trazodone anxiety and sedation scales were compared to confirm the efficacy of trazodone.\(^13,19,20\) All study participants were kept in a consistent environment throughout the duration of the study to minimize the impact of variations in environment. Consistently across each neurologic examination per dog, background noise and the presence of uninvolved individuals were both kept at a minimum. Owners were not present for the examinations aside from 1 dog, the owner of which was the neurologist performing the examination. In between neurologic examinations, each dog remained in the same cage it had been placed in before the first examination.

After all videos of the neurologic examinations had been recorded, the video files were randomized and given a numerical code before being blindly reviewed and scored by a second veterinary neurologist (NZ). The time and date stamps of each video were removed before providing the videos to this blinded clinician. For all videos except 1, the sound was muted when reviewed; for 1 dog, the before and after videos were specifically requested to be viewed with audio, because this component was important for interpretation. Each dog served as its own control throughout our comparisons between pre- and post-trazodone neurologic examination.

2.3 | Neurologic examination

The order of the neurologic examination performed was as follows for each dog: mentation, cranial nerves, postural reactions (PR), reflexes,
palpation, range of motion, and gait analysis. The videos were scored by the masked reviewer (NZ) using the preassigned numerical values per category (Table 1).

2.4 | Statistical analysis

For our study population, findings were summarized as mean and SD for normally distributed data (time between examinations) and median with range for non-normally distributed data (age, body weight, dosage). The results of each dog’s pre- and post-trazodone sedation and anxiety scores were compared using a 2-tailed paired t test to determine efficacy and level of effect of trazodone. A statistical analysis program (GraphPad Prism) was used for calculations. A P-value of <.05 was considered significant for all tests.

3 | RESULTS

3.1 | Study population

The study included 32 dogs (16 castrated male dogs, 15 spayed female dogs, and 1 intact female dog). The median age was 3 years (range, 1-6 years) and the median body weight was 22.85 kg (range, 4.0-37.7 kg). The mean time between administration of trazodone and performance of the second neurologic examination was 147 ± 28.9 minutes (2 hours, 27 minutes). The median dosage of trazodone administered was 7.60 mg/kg (range, 6.25-8.60 mg/kg). One dog was excluded from the study because of aggressive behavior elicited by attempts at restraint and neurological examination was not possible.

Breed included Australian Shepherd, Beagle/Basset Hound Cross, Border Collie, Brittany Spaniel, Cattle Dog Mix, Chihuahua, Collie, Dachshund Mix, French Bulldog (n = 2), German Shorthair Pointer, Golden Retriever (n = 4), Irish Setter, Labrador/Golden Cross, Labrador Mix (n = 2), Labrador Retriever (n = 3), Miniature Poodle Mix, Mixed Breed, Pembroke Welsh Corgi (n = 2), Pit bull Terrier, Pointer Mix, Portuguese Water Dog, Pug, Shepherd Mix, Toy Australian Shepherd. Each dog breed represented 1 dog of that breed, unless otherwise specified.

3.2 | Anxiety and sedation scales

The level of sedation was significantly higher post-trazodone compared to pre-trazodone (P < .0001; Figure 1). The level of anxiety was also significantly lower post-trazodone compared to pre-trazodone (P < .0001; Figure 1a, b).

3.3 | Neurologic examination

Eleven of 32 dogs had at least 1 neurologic abnormality identified on initial (pre-trazodone) neurological examination: 7 dogs had delayed PR deficits involving at least 1 limb, 1 dog had moderate cervical pain with delayed PR deficits of all 4 limbs, 2 dogs had decreased withdrawal reflexes bilaterally, 1 dog had an absent patellar reflex unilaterally, and 1 dog was obtunded. No cranial nerve abnormalities were identified on either the pre- or the post-trazodone neurologic examinations. One dog responded painfully to spinal palpation with no change in severity or location detected between pre- versus post-trazodone examination. One dog had mild ataxia post-trazodone. Two dogs had mildly reduced withdrawal reflexes on 1 hind limb in the

### TABLE 1 Protocol for scoring each aspect of the neurologic examination

| Component of neurologic examination | Numerical score per exam component (maximum score: 39) |
|------------------------------------|------------------------------------------------------|
| Mounting | 0 | 1 | 2 | 3 |
| Bar (0a) QAR (0b) | Obtunded | Stuporous | Comatose |
| Cranial nerves | Normal (all) | Abnormal (any) |
| Postural reactions (1 score per limb) | Normal | Mildly delayed | Moderately delayed | Absent |
| Ataxia | Normal | Mild | Moderate |
| Paresis | Withdrawal (1 score per limb) | Normal | Reduced | Absent |
| Patellar (1 score per limb) | Normal | Reduced | Exaggerated | Absent |
| Perineal | Present | Absent |
| Cutaneous trunci | Present | Absent |
| Spinal reflexes | Normal | Absent |
| Withdrawal (1 score per limb) | Normal | Reduced | Absent |
| Patellar (1 score per limb) | Normal | Reduced | Exaggerated | Absent |
| Perineal | Present | Absent |
| Cutaneous trunci | Present | Absent |
| Spinal palpation | Normal | Abnormal |
| Range of motion | Tail | Normal | Abnormal |
| Cervical | Normal | Abnormal |

Note: Each category was tested and interpreted in identical sequence across all examinations. A total score of 0 would be considered a normal neurologic examination. The scores for each category were summed to yield an overall score for each neurologic examination (pre- and post-trazodone).

*The masked clinician was instructed to characterize any ataxia appreciated as either proprioceptive, cerebellar, or vestibular.
3.3.1 | Mentation

Mentation changes were noted in 9 of 32 dogs (28%) when comparing their pre- versus post-trazodone examinations (Table 2). None of the neurologic examination scores for any dog were altered by the changed mentation states on the post-trazodone examination. Twenty-four dogs were scored as bright, alert, and responsive (BAR) in the pre-trazodone examination, and 18 (75%) of these dogs remained BAR on the post-trazodone examination. The remaining 6 dogs (25%) were scored as quiet, alert and responsive (QAR) on the post-trazodone examination. Seven dogs (21%) were scored as QAR in the pre-trazodone examination. Of these, 4 (57%) remained QAR whereas 3 (43%) were scored as BAR in the post-trazodone examination. One dog (14%) was scored as obtunded in both the pre- and post-trazodone assessments.

3.3.2 | Postural reactions

Proprioception was assessed in all dogs by way of the paw replacement test, and results are shown in Table 3. Because of patient temperament or inconsistent results on paw replacement, several dogs required additional testing of proprioception using the hopping response. Seven dogs (22%) developed new or worsening PR deficits on the post-trazodone assessment. Six of those dogs had PR deficits post-trazodone in limbs that were initially normal; 1 dog had initially mild PR deficits in all limbs that progressed to moderate deficits post-trazodone. Seven of 32 dogs (22%) showed PR deficits on the pre-trazodone assessment. Of those, 3 dogs experienced normalization (improvement/resolution) of those initial delays on their post-trazodone assessment. Another 3 dogs had PR deficits that were unchanged in the pre- and post-trazodone examinations, and 1 dog had a mild unilateral PR deficit in one hind limb pre-trazodone but mild PR deficits in both hind limbs on the post-trazodone assessment. The latter dog therefore also was included with the 6 dogs with new PR deficits.

3.3.3 | Neurologically normal dogs

Of the 31 dogs that participated in the study, 22 had completely normal neurologic examinations before administering trazodone (71%).
Four of these 22 dogs (18%) had changes on post-trazodone neurologic examination, all of which manifested new PR deficits. Two of these dogs developed mild PR deficits in 2 limbs, and 1 dog developed moderate PR deficits in 2 limbs. Additionally, 3 of these 22 dogs were initially QAR but became BAR post-trazodone; 2 were initially BAR but became QAR post-trazodone.

### DISCUSSION

Our findings indicate that most dogs do not experience clinically relevant changes or progression of abnormalities in neurologic examinations after PO trazodone administration. However, 20% of dogs did exhibit alterations in their neurologic examinations, but these changes were mild. Of the dogs that were neurologically normal before trazodone and developed neurologic deficits post-trazodone, the changes were limited only to new PR deficits in 1 or 2 limbs. The clinically relevant changes identified were in the form of new or worsened PR deficits when considering the entire sample collectively. Overall, these changes were mild in nature and, in most cases, involved only 1 limb. Nonclinically relevant changes in mentation were appreciated in <20% of dogs.

Seven dogs (of 32) in the study displayed new or worsened paw replacement deficits after trazodone administration. This change is perhaps explained by trazodone’s cortical effects. Given the involvement of the cerebral cortex in the pathway for conscious proprioception, it is possible that the effects of trazodone on the telencephalon precipitated the PR deficits newly identified on the post-trazodone examinations.

After PO trazodone administration, 18.8% of the dogs experienced a change in attitude from BAR to QAR, remaining alert and responsive. This finding is consistent with previous studies showing a decrease in overall level of excitation and increased calmness. It is possible that the effects of trazodone on the telencephalon precipitated the PR deficits newly identified on the post-trazodone examinations.

A major limitation of our study is that despite our inclusion criteria that all dogs be normal and healthy according to their owners, several dogs (n = 11) were found to have abnormalities on baseline (pretrazodone) neurologic examination. However, we chose to include these dogs because the situation is representative and clinically relevant for the population of dogs seen by veterinarians. Subtle deficits detected on a neurologic examination performed by a neurologist are easily overlooked by clients and practicing veterinarians who are not performing neurologic examinations regularly. Additionally, each dog received a single neurologic examination for each assessment, which increased the possibility of spurious findings or abnormalities that may not actually be abnormal or consistent.

Future studies should assess the effects of trazodone on the neurologic examination for dogs with neurologic abnormalities such as intracranial, neuromuscular or myelopathic conditions. This approach may help characterize how trazodone alters the neurologic examination based on prerecognized neurolocalizations. Additionally, it would

### TABLE 3

Dogs with initial postural reaction (PR) deficits were identified on the pre-trazodone assessment but normal postural reactions were observed post-trazodone were classified as having "normalized PR".

| Changes in postural reactions (PR) observed following trazodone administration | New PR Deficits | Progressive PR Deficits | Normalized PR | Normal PR-Static | Abnormal PR-Static |
|---|---|---|---|---|---|
| Number of dogs | 6 | 1 | 3 | 21 | 3 |
| Ratio of dogs affected | 6/32 | 1/32 | 3/32 | 21/32 | 3/32 |
| Percentage of total dogs | 18.8% | 3.1% | 9.4% | 65.6% | 9.4% |

Note: Normal PR-Static indicates the dogs who had consistent normal PRs across both assessments, while Abnormal PR-Static indicates the dogs who had consistently abnormal PRs across both assessments. Progressive PR includes dogs who had PR deficits noted on the pre-trazodone assessment that worsened post-trazodone. New PR Deficits includes dogs who had normal PRs pre-trazodone but abnormal PRs post-trazodone, in one or more limbs. Percentages do not summate to 100% because some dogs were represented more than once for variations across their limbs.
be prudent to investigate whether trazodone alters the neurologic examination in dogs that are systemically or critically ill. Such dogs are more likely to warrant hospitalization and subsequent anxiolytic treatment, in addition to being more prone to the development of neurologic abnormalities as a result of their systemic disease. Having a basis on which to gauge the likelihood that new-onset neurologic signs are a result of trazodone versus progression of the disease may be helpful in these circumstances.

In conclusion, for situations in which a dog urgently requires a neurologic examination but has received PO trazodone, the findings of our study are not sufficient to preclude the clinician from performing and interpreting a complete neurologic examination. However, in these circumstances, caution should be exercised when interpreting any mild PR deficits found on neurologic examination. We did not find evidence to suggest drugs experience any clinically relevant change in mention after trazodone administration. If the clinician needs to discern whether any mild deficits identified on the neurologic examination were the result of the trazodone versus true manifestations of a neurologic lesion, it is recommended that the neurologic examination be repeated at a later time when the patient has not received trazodone.

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CONFLICT OF INTEREST DECLARATION
Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION
Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION
This study protocol was approved by the IACUC of the University of Wisconsin - Madison, School of Veterinary Medicine (IACUC-V006493-A02).

HUMAN ETHICS APPROVAL DECLARATION
Authors declare human ethics approval was not needed for this study.

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REFERENCES
1. Stanford TL. Behavior of dogs entering a veterinary clinic. Appl Anim Ethol. 1981;7(3):271-279. doi:10.1016/0304-3762(81)90083-3
2. Hekman J, Karas A, Sharp C. Psychogenic stress in hospitalized dogs: cross species comparisons, implications for health care, and the challenges of evaluation. Animals. 2014;4(2):331-347. doi:10.3390/ani4020331
3. Glaser R, Kiecolt-Glaser JK. Stress-induced immune dysfunction: implications for health. Nat Rev Immunol. 2005;5(3):243-251. doi:10.1038/nri1571
4. Kemeny ME, Schedlowski M. Understanding the interaction between psychosocial stress and immune-related diseases: a stepwise progression. Brain Behav Immun. 2007;21(8):1009-1018. doi:10.1016/j.bbi.2007.07.010
5. Dhabhar FS. Enhancing versus suppressive effects of stress on immune function: implications for immunoprotection and immunopathology. Neuroimmunomodulation. 2009;16(5):300-317. doi:10.1159/000216188
6. Gruen ME, Roe SC, Griffith E, Hamilton A, Sherman BL. Use of trazodone to facilitate postsurgical confinement in dogs. J Am Vet Med Assoc. 2014;245(3):296-301. doi:10.2460/javma.245.3.296
7. Riemer S, Hertibler C, Windschneider J, Pratsch L, Archant C, Affenzeller N. A review on mitigating fear and aggression in dogs and cats in a veterinary setting. Animals. 2021;11(1):158. doi:10.3390/ani11010158
8. Erickson A, Harbin K, MacPherson J, Rundle K, Overall KL. A review of pre-appointment medications to reduce fear and anxiety in dogs and cats at veterinary visits. Can Vet J. 2021;62(9):952-960.
9. Gruen ME, Sherman BL. Use of trazodone as an adjunctive agent in the treatment of canine anxiety disorders: 56 cases (1995-2007). J Am Vet Med Assoc. 2008;233(12):1902-1907. doi:10.2460/javma.233.12.1902
10. Gilbert-Gregory SE, Stull JW, Rice MR, Herron ME. Effects of trazodone on behavioral signs of stress in hospitalized dogs. J Am Vet Med Assoc. 2016;249(11):1281-1291. doi:10.2460/javma.249.11.1281
11. Gruen ME, Roe SC, Griffith EH, Sherman BL. The use of trazodone to facilitate calm behavior after elective orthopedic surgery in dogs: results and lessons learned from a clinical trial. J Vet Behav. 2017;22:41-45. doi:10.1016/j.jveb.2017.09.008
12. Andrade C. Stahl’s essential psychopharmacology: neuroscience basis and practical applications. Mens Sana Monogr. 2010;8(2):146. doi:10.4103/0973-1229.58825
13. Jay AR, Krotscheck U, Parsley E, et al. Pharmacokinetics, bioavailability, and hemodynamic effects of trazodone after intravenous and oral administration of a single dose to dogs. Am J Vet Res. 2013;74(11):1450-1456. doi:10.2460/javma.74.11.1450
14. Riviere JE, Papich MG, eds. Veterinary Pharmacology and Therapeutics. Hoboken, NJ: John Wiley & Sons; 2018.
15. Plumb D. Plumb’s Veterinary Drug Handbook. Hoboken, NJ: John Wiley & Sons; 2018.
16. Grint NJ, Burford J, Dugdale AHA. Does pethidine affect the cardiovascular and sedative effects of dexmedetomidine in dogs? J Small Anim Pract. 2009;50(2):62-66. doi:10.1111/j.1748-5827.2008.00670.x
17. Wagner MC, Hecker KG, Pang DSI. Sedation levels in dogs: a validation study. BMC Vet Res. 2017;13(1):110. doi:10.1186/s12917-017-1027-2
18. Mills DS, Mueller HW, McPeake K, Engel O. Development and psychometric validation of the Lincoln canine anxiety scale. Front Vet Sci. 2020;7:171. doi:10.3389/fvets.2020.00171
19. Herron ME, Shreyer T. The pet-friendly veterinary practice. Vet Clin N Am. 2014;44(4):451-481. doi:10.1016/j.cvsm.2014.01.010
20. Gruen M. Trazodone: for behavior and beyond (oral presentation). Published August 2012.
21. de Lahunta A, Glass E, Kent M. De Lahunta’s Veterinary Neuroanatomy and Clinical Neurology. Saunders. Philadelphia, PA: Elsevier; 2020.
22. Murphy LA, Barletta M, Graham LF, Reichl LJ, Duxbury MM, Quandt JE. Effects of acepromazine and trazodone on anesthetic induction dose of propofol and cardiovascular variables in dogs undergoing general anesthesia for orthopedic surgery. J Am Vet Med Assoc. 2017;250(4):408-416. doi:10.2460/javma.250.4.408
23. Lind AK, Hydbring-Sandberg E, Forkman B, Keeling LJ. Assessing stress in dogs during a visit to the veterinary clinic: correlations between dog behavior in standardized tests and assessments by veterinary staff and owners. J Vet Behav. 2017;17:24-31. doi:10.1016/j.jveb.2016.10.003
24. Csoltova E, Martineau M, Boissy A, Gilbert C. Behavioral and physiological reactions in dogs to a veterinary examination: owner-dog interactions improve canine well-being. *Physiol Behav*. 2017;177:270-281. doi:10.1016/j.physbeh.2017.05.013

25. Döring D, Roscher A, Scheipl F, Küchenhoff H, Erhard MH. Fear-related behaviour of dogs in veterinary practice. *Vet J*. 2009;182(1):38-43. doi:10.1016/j.tvjl.2008.05.006

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