

Trazodone

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Trazodone can reliably and safely induce sedation and anxiolysis in dogs and cats, making it a useful pharmacologic agent beyond the treatment of behavior problems.

INDICATIONS

Trazodone has been clinically used in both dogs and cats; however, its use has been more extensively researched in dogs.

- ▶ Situational anxiety related to
 - Separation¹
 - Noise phobia (eg, fireworks, thunderstorms)¹
 - Veterinary visits²
 - Hospitalization³
 - Travel
- ▶ Postoperative confinement³
- ▶ Adjunct therapy used in combination with other psychopharmaceutical agents to treat anxiety-related behavioral problems (eg, fearful behavior toward humans or other animals)¹

PHARMACOLOGY & CLINICAL APPLICATIONS

Trazodone is an atypical antidepressant used to treat anxiety and depression by acting as a serotonin antagonist/reuptake inhibitor (SARI).

- ▶ Trazodone is most often prescribed as an augmenting agent to selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs).
- ▶ It globally increases serotonin levels by blocking presynaptic reuptake in humans⁴ and presumably in dogs and cats.
 - Higher doses (see **Recommended starting dose**, next page) are typically required to achieve reuptake inhibition.⁴
- ▶ The drug also readily antagonizes postsynaptic serotonin 2A and 2C receptors (5-HT_{2A} and 5-HT_{2C}, respectively), thereby inhibiting glutamate release and stimulating dopamine and norepinephrine release in the prefrontal cortex.⁴

5-HT_{2A} = serotonin 2A receptor

5-HT_{2C} = serotonin 2C receptor

SARI = serotonin antagonist/reuptake inhibitor

SSRI = selective serotonin reuptake inhibitor

TCA = tricyclic antidepressant

- ▶ In addition to antagonizing serotonin receptors, trazodone antagonizes histamine 1 (H₁) and α₁-adrenergic receptors, resulting in a sedative-hypnotic effect.⁴
 - Sedation may be achieved at lower doses as compared with doses needed for treatment of anxiety (see **Recommended starting dose**).⁴
 - May be used to facilitate postsurgical confinement³
 - Could also promote calm behavior in other situations (eg, travel/transport, nighttime restlessness associated with cognitive dysfunction)

Recommended starting dose for dogs is 3-7 mg/kg PO once to twice a day.⁵ If the drug is used to treat situational anxieties, the same dose can be administered as needed 1 to 2 hours before the anticipated event; that dose may be further increased to effect.⁵

- ▶ When prescribing trazodone for the first time, instruct clients to administer a test dose at home in a quiet and calm environment to monitor for
 - Time to onset of sedation or behavioral calming
 - Duration of effect
 - Adverse events and side effects
- ▶ If behavioral calmness and/or anxiety are not achieved, the dose or administration frequency may be increased to effect.
- ▶ Studies have reported a large PO dose range of up to 14 mg/kg once a day (for as-needed administration only) and 19.5 mg/kg once a day (for both daily and as-needed administration).¹

In dogs, latency to onset is typically <2 hours following oral administration, permitting use as a faster-acting sedative/anxiolytic for situational anxiety.^{1,3}

- ▶ Anxiety-provoking situations that may benefit from trazodone treatment include veterinary visits, travel/transport, separation anxiety, and noise phobias associated with fireworks or thunderstorms.
 - Oral trazodone may also be administered by veterinary staff to anxious hospitalized patients as long as there are no contraindications.
- ▶ Preemptively administer trazodone 1 to 2 hours before onset of anxiety to prevent emotional sensitization.
- ▶ Presence of food in the upper GI tract may delay absorption.⁶
- ▶ For dogs, trazodone may be used on an as-needed basis for situational anxieties, as daily medication administered every 8 to 10 hours, or when a combination of daily and

as-needed administration is required.¹

- Duration of effect is variable.
 - Median duration of action when used to facilitate postsurgical calming was ≥4 hours.³

A recent study in cats showed that trazodone was well-tolerated and caused sedation at doses of 50, 75, and 100 mg.²

- ▶ Cats achieved peak sedation at 2 to 2.5 hours after oral administration.²
- ▶ Trazodone may be a good alternative fast-acting anxiolytic in cats that exhibited adverse events to benzodiazepines (eg, lorazepam).
- ▶ It may be used in similar situations as for dogs.
- ▶ Recommended starting dose in adult cats⁷
 - 25 mg/cat
 - Can be titrated to effect

ADVERSE EVENTS & WITHDRAWAL EFFECTS

Adverse events associated with oral administration of trazodone in dogs and cats are typically mild and well-tolerated.

- ▶ Potential effects include^{1,2,6}
 - Sedation
 - Ataxia
 - GI effects (eg, vomiting, diarrhea)
 - Increase or decrease in appetite
 - Agitation
 - Tachycardia
 - Behavioral disinhibition
- ▶ IV administration of trazodone has only been investigated in dogs and is not recommended, as doing so may trigger aggressive behavior in some dogs.⁶
 - An injectable form of trazodone is not commercially available.

Tolerance, withdrawal effects, and dependence have not been reliably demonstrated.

- ▶ As a precaution, patients may be tapered off medication to

Patients may be tapered off medication to reduce the likelihood of withdrawal effects.

CLIENTS SHOULD BE COUNSELED ABOUT THE RISK AND CLINICAL SIGNS ASSOCIATED WITH SEROTONIN SYNDROME.

If clinical signs are seen, clients should contact their veterinarian immediately or take their pet for emergency care. The pet should *not* receive any additional serotonergic medications until assessed by a veterinarian. Treatment is supportive and targeted toward addressing hyperthermia, as well as cardiovascular, GI, and neurologic signs.

For additional information on the diagnosis and treatment of serotonin syndrome, see **Serotonin Syndrome** in the October 2013 issue of *Clinician's Brief* or on cliniciansbrief.com.

reduce the likelihood of withdrawal effects and to observe the patient for increased anxiety while trazodone is withdrawn.

CAUTIONS

Because of potential risk for serotonin syndrome, use caution when combining trazodone with other serotonergic agents and/or monoamine oxidase inhibitors (MAOIs).

- ▶ Although trazodone is most often used to augment SSRIs and TCAs, caution must be taken when it is administered with these other agents.
 - Signs of serotonin syndrome include
 - Cardiovascular changes (ie, tachycardia, bradycardia, hypertension, arrhythmias)
 - Tachypnea
 - Hyperthermia
 - Nervous system effects (ie, disorientation, weakness, hyperexcitability, agitation, hyperreflexia, hyperesthesia, tremors, seizures, coma)
 - GI changes (ie, vomiting, diarrhea, hypersalivation)
 - Signs can lead to death.
- ▶ Close patient monitoring via recheck appointments and/or client communication is recommended.

MAOI= monoamine oxidase inhibitor

SSRI = selective serotonin reuptake inhibitor

TCA = tricyclic antidepressant

When writing prescriptions or discharge instructions for trazodone, do not mistake *trazodone* for *tramadol*.

- ▶ On the prescription label, specify *FOR ANXIETY* as treatment indication.
- ▶ Educate clients about the difference between trazodone and tramadol, particularly if the pet receives both medications.
- ▶ To minimize prescription errors, use exaggerated lettering, also known as Tall Man Lettering, to distinguish look-alike medications (eg, traZODone vs traMADol).⁸

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References

1. Gruen ME, Sherman BL. Use of trazodone as an adjunctive agent in the treatment of canine anxiety disorders: 56 cases. *JAVMA*. 2008;233(12):1902-1907.
2. Orlando JM, Case BC, Thomson AE, Griffith E, Sherman BL. Use of oral trazodone for sedation in cats: a pilot study. *J Feline Med Surg*. 2015;18(6):476-482.
3. Gruen ME, Roe SC, Griffith E, Hamilton A, Sherman BL. Use of trazodone to facilitate postsurgical confinement in dogs. *JAVMA*. 2014;245(3):296-301.
4. Stahl SM. Mechanism of action of trazodone: a multifunctional drug. *CNS Spectr*. 2009;14(10):536-546.
5. Perrin C, Seksel K, Landsberg GM. Appendix: drug dosage chart. *Vet Clin North Am Small Anim Pract*. 2014;44(3):629-632.
6. 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. *AJVR*. 2013;74(11):1450-1456.
7. Sueda KLC, Cho J. Unpublished observations and clinical data, to VCA West Los Angeles Animal Hospital; accumulated clinical evidence as of March 2016.
8. U.S. Food and Drug Administration. Name Differentiation Project; FDA-approved established drug names with recommended tall man letters; <http://www.fda.gov/drugs/drugsafety/medicationerrors/ucm164587.htm>. Accessed June 2016.