

BEYOND THE FRONT LINE: TRAZODONE AND OTHER ANCILLARY TREATMENTS FOR ANXIETY

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Canine and feline anxiety disorders are a considerable problem for owners, and the veterinarians they look to for help. Many owners consider their veterinarian to be an important resource when faced with a behavior problem such as anxiety. The impact of anxiety disorders in pets is also evident in the variety of treatment products designed to address the problem. Two of the three FDA approved medications for use in veterinary behavioral medicine are for separation anxiety in dogs, and shelves are full of supplements, scents, accessories, and toys to prevent or improve anxiety.

Improved detection, diagnosis, and treatment of anxiety disorders in dogs and cats have led to increased welfare for many patients suffering from anxiety. Still, for many patients, treatment with a first-line agent such as a tricyclic antidepressant (TCA) or selective serotonin reuptake inhibitor (SSRI) is not enough. Often, an adjunctive medication is needed, in conjunction with a medical workup and behavioral plan. In this lecture, we will discuss several of the adjunctive medications for use in anxiety disorders. Special attention will be paid to one medication, trazodone hydrochloride, which has been gaining popularity for treatment of a variety of conditions in dogs.

Trazodone

Trazodone was first developed in Italy in the 1960s, and became available for use in the United States in the early 1980s as Deseryl®. It was developed as an antidepressant, anxiolytic, and anti-compulsive agent, however its use in humans for these indications was supplanted by newer antidepressants that lacked the drowsiness reported with trazodone administration. Currently, trazodone is most commonly prescribed in human medicine as a hypnotic for treating both primary insomnia and residual insomnia in patients taking an SSRI or SNRI. At low doses, trazodone has been shown to increase slow wave sleep. Recently, there has been renewed interest in trazodone as an antidepressant option for certain patients.¹ There is also some indication that trazodone is useful for decreasing some of the agitation and behavioral signs such as irritability in patients with Alzheimer's disease.

Mechanism of action

Trazodone is classified as a serotonin antagonist/reuptake inhibitor (SARI). At low to moderate doses, trazodone mainly acts to antagonize postsynaptic 5HT_{2A} receptors, as well as histaminic (H₁) and adrenergic (alpha₁) receptors, which may account for some of its hypnotic effects. At higher doses, trazodone also acts as an antagonist at postsynaptic 5HT_{2C} receptors as well as blocking the serotonin transporter (SERT) on the presynaptic neuron.³ Its antidepressant activity is thought to be due to the combination of SERT inhibition and 5HT_{2A} antagonism. There is some evidence⁴ that

trazodone works synergistically when given with an SSRI. Trazodone has one active metabolite, meta-chloro-phenyl piperazine (m-CPP), which is also active at 5HT_{2C} receptors, and may account for the uncommon adverse effects of headache and nausea that sometimes follow trazodone administration. Trazodone has minimal effects on muscarinic cholinergic receptors, so has considerably fewer anticholinergic side effects than the tricyclic antidepressants (TCAs).

Pharmacokinetics

In humans, trazodone is rapidly absorbed after oral dosing, with peak blood levels occurring one hour after administration if taken on an empty stomach, and two hours after dosing with food. It then undergoes extensive hepatic metabolism, with less than 1% being excreted unchanged in feces or urine. Trazodone's elimination pattern has been described as biphasic, with a fast phase of three to five hours followed by a slower phase of five to nine hours. Trazodone is converted to its metabolite (m-CPP) by CYP450 3A4, which is further metabolized by CYP450 2D6. Studies are needed to detail the pharmacokinetic pattern in dogs.

Side effects

In humans, reported side effects include somnolence, dizziness, appetite changes, and constipation. A rare side effect in human males is priapism, occurring at a rate of approximately 1/10,000. This side effect has not been reported in dogs, however experience in unneutered males is limited. In two studies conducted at NCSU, side effects were generally mild, and included GIT signs, sedation, excitement, and panting.

Dosage and administration

Trazodone is available as a generic medication and comes as tablets in 50mg, 100 mg, 150 mg, and 300 mg. It can be given with or without food. Based on owner reports, the onset of action in dogs is approximately 1 hour, so if using as an episodic therapy, such as for storm phobia or travel anxiety, dosing well in advance of the stimulus is recommended.

Trazodone was used, in a recent study (unpublished results), as a single agent at doses of 5-30 mg/kg/day (divided q8-12 hours). The mean dose for this population was 15 mg/kg/day. When used as an adjunctive medication, starting doses for trazodone are typically lower, and dose titration used to achieve clinical success. Dogs may require incremental dose increases as they become tolerant to the effects of trazodone.

Drug interactions and cautions

Trazodone has a large safety margin for the majority of our canine patients. As an antidepressant, trazodone is prescribed in humans at up to 600 mg/d. The LD₅₀'s for mice, rats, and rabbits are 610 mg/kg, 486 mg/kg, and 560 mg/kg respectively.

Trazodone is frequently used in combination with other serotonergic medications. Several studies have shown that a combination of trazodone with an SSRI may lead to synergistic effects on serotonin, and that the combination is generally safe. Our research on trazodone use in dogs suggests that the use of trazodone as an adjunctive

medication, in combination with a TCA or SSRI, is well tolerated. In our practice, we will use the baseline medication (TCA or SSRI) at established dose ranges, and add trazodone as a PRN or daily medication.

Trazodone appears to be well tolerated when co-administered with many routine medications such as flea, tick, and heartworm preventatives. However, concurrent use of any MAOI inhibitors should be avoided, and includes products containing amitraz. Plasma levels of trazodone may be increased by any medications that inhibit the CYP450 3A4 system such as ketoconazole and itraconazole. While trazodone has been shown to have less cardiotoxicity than TCA's,⁵ and has been shown to have little effect on cardiac function in anesthetized dogs,⁶ caution should be used when considering trazodone in cases with significant baseline cardiac abnormalities. In a retrospective study of dogs on trazodone,² no adverse events were reported in dogs undergoing routine anesthetic protocols while taking trazodone, however, the combination of trazodone with general anesthetic agents has not been studied.

Serotonin syndrome is a potential complication of an overdose of a serotonergic medication, or concurrent use of multiple serotonergic agents. Reports of serotonin syndrome with trazodone use are uncommon, and limited to individual case reports, however, patients on multiple serotonergic medications must be monitored for signs of serotonin syndrome including agitation, tachycardia, and hyperthermia.

Benzodiazepines

Benzodiazepines have been widely used in veterinary medicine. They function to increase the action of GABA-A receptors by acting as positive allosteric modulators, leading to decreased neuronal transmission in the CNS. They have the benefits of rapid onset of action and potent anxiolytic action, and can be especially useful for episodic anxieties or while starting a slower-onset anxiolytic like a TCA or SSRI. There are many members of this class, with differing profiles. Several members of this class, including lorazepam, oxazepam, and clonazepam, have no active metabolites and may be better tolerated by geriatric patients or those with mild hepatic dysfunction.

Benzodiazepines are contraindicated in some cases. Aggressive behavior, especially fear based, has been listed as a contraindication to benzodiazepine use in dogs due to the risk of behavioral disinhibition. In cats, oral diazepam has been associated with idiopathic hepatic necrosis. In animals with any hepatic or renal insufficiency, a benzodiazepine without active metabolites is recommended.

Some animals may show paradoxical excitement with benzodiazepines, which may respond to a dose change. We typically see this with alprazolam, though this bias has not been well described. We recommend starting benzodiazepines at the low end of the dose range, and titrating up as needed. In cases where benzodiazepines have been used long term, animals must be slowly weaned off in order to avoid withdrawal symptoms.

Clonidine

This alpha-2 agonist has historically been used in humans as an anti-hypertensive agents, and (off-label) for the treatment of PTSD, ADHD, and impulsivity. It works by blocking NE release through activation of alpha-2 receptors on presynaptic neurons in the locus ceruleus.⁷ It has a fairly long half-life in humans, but pharmacokinetic data in dogs is needed. A recent study has shown that clonidine may be effective in treatment of canine anxiety disorders. Dogs in the study were maintained on baseline medications, and given clonidine as a PRN treatment at 0.01mg/kg initially, with increases up to 0.05mg/kg (up to total dose of 0.9mg) as needed. Client reports indicated that the time to effect was approximately 2 hours, and duration of effect was 6 hours. While side effects were rare in this study, the authors caution to watch for sedation and hypotension in patients taking clonidine.

Buspirone

This serotonin 1A partial agonist is used in humans as an anxiolytic and as an adjunct for treatment of depression. It also has activity as an antagonist of dopamine D2 receptors. It is relatively short acting, requiring BID-TID dosing, and has a relatively long lead –in period prior to clinical effect (up to 6 weeks). In humans, it may cause some nausea and dizziness. However, in dogs and cats, there are very few reports of side effects, and it is a reasonable choice for use in older patients.

Gabapentin

Gabapentin is structurally similar to GABA, though it may actually work on glutamate receptors. It has been used for generalized anxiety, especially when neuropathic pain is a concern. Doses of 20-60 mg/kg/day divided up to TID have been reported.

Nutraceuticals

Anxitane

Anxitane (L-theanine) is an amino acid extracted from green tea. The commercial formulation has been found to be highly palatable for dogs and cats. According to company literature, Anxitane works by increasing the concentration of GABA, increasing serotonin and dopamine, and inhibiting binding of glutamate receptors. It has been shown to decrease some fear responses (especially fear of unfamiliar people) in a group of laboratory dogs, and had no adverse effects observed. In cats, it is recommended for fear related aggression, fear of people, and anxiety.

Zylkene

Zylkene (tryptic bovine alpha-S1-casein hydrolysate) is derived from a milk protein called alpha-casozepine. The molecule is structurally similar to GABA and has some affinity for GABA-A receptors. The manufacturer's highlights are that it can be given once a day, is lactose free, easy to dose, and has not been associated with any side effects. Studies on efficacy are lacking, but it has been used in cats with social phobia and fear, and in dogs with anxiety.

Others

Pheromones

Pheromones may be used to influence the emotional state of animals. They are chemicals released from external surfaces of the body, such as the sebaceous cheek glands in cats, which affect the behavior of other individuals. There are synthetic analogs of several pheromones that are available for use in animals. For dogs and cats, these include the feline facial pheromone (Feliway®), the canine intramammary sulcal pheromone (DAP®), and the pheromones in the Nuturecalm collars. According to manufacturer studies of the Nuturecalm collars, these collars emit a larger amount of pheromone and last longer than other commercially available collars. Anecdotally, many cat owners have observed decreases in anxiety and aggression in cats wearing these collars.

Wraps

Clinical use suggests promising results for some dogs when using a snug fitting body wrap. Two such wraps are commercially available: the Thundershirt and Anxiety Wrap. These appear, in the author's opinion, to be especially useful for episodic anxieties such as thunderstorm phobia. Recently, a cat product has become available as well.

Common indications in pets

For all cases in which medications are prescribed, a full medical work up and behavioral plan are needed. Below are a few of the common indications for adjunctive medication use in dogs, and some tips for how we use it in practice.

Storm phobia: First line – TCA or SSRI

Trazodone has been used in the treatment of storm phobia as a single agent in mild cases, or as an adjunct in more severe cases. We typically prescribe a baseline TCA or SSRI, and add trazodone for PRN storm anxiety. Owners are instructed to give the trazodone at the first sign of storm anxiety (not the first sign of a storm) or if they will be gone and a storm is predicted.

Benzodiazepines are also often useful in the treatment of storm phobia. Like trazodone, they are given at the first sign of storm anxiety, or if a storm is predicted. In severe cases, a benzodiazepine may be used with trazodone and a baseline medication.

Separation anxiety: First line – TCA or SSRI

Trazodone and benzodiazepines are used in a similar way as in storm phobia, but patients are generally prescribed them as a once or twice daily medication, with an additional dose to be given if there is a departure that is outside the routine. Owners are instructed to give the medications at least 45-60 minutes prior to departures. Buspirone is another option for treatment of separation anxiety.

Travel anxiety/veterinary visits: Trazodone may be useful in alleviating signs of anxiety in dogs on car rides or for veterinary visits. In these cases, we recommend that owners try the medication at home first, in order to observe their dog's reaction, and time to

effect. Doses of 3-7 mg/kg may be used (starting at the low end of the dose range, and increasing as necessary for effect).

Anxitane or benzodiazepines may be helpful in these cases as well.

Post-operative exercise restriction: Trazodone has been used to facilitate calming in dogs undergoing exercise restriction while healing from surgery, especially orthopedic or neurologic surgical procedures. When using with tramadol immediately post-operatively, a lower dose (3-5mg/kg q12-24) is used, and this may be increased when the tramadol course is completed.

Feline anxieties – including urine marking as symptom

Many treatments for urine marking are designed to decrease anxiety and arousal. In mild cases, a pheromone diffuser or collar may be useful. Composure® (not discussed) has been mentioned to the author as a helpful addition to the pheromone collar. In very severe cases, a benzodiazepine without active metabolites may be useful, but must be used following risk discussion with the owner.

Summary

Many ancillary treatments have shown usefulness in treating canine and feline anxiety disorders. Trazodone has become widely used in veterinary medicine for treatment of a diverse group of canine conditions. Its wide dose range and flexible dosing schedule make it a valuable addition to our arsenal for treatment in behavioral medicine. Use of these medications and treatments can, with a comprehensive behavioral plan, enhance clinical improvement in behavior cases.

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