A review of pre-appointment medications to reduce fear and anxiety in dogs and cats at veterinary visits

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Abstract — This review focuses on pre-appointment medications used to decrease fear and anxiety in dogs and cats related to veterinary visits. A review of the literature revealed data on 4 medications from 4 medication classes that have been used to ameliorate acute situational fear and anxiety in dogs and cats: gabapentin, trazodone, oral transmucosal dexmedetomidine, and alprazolam. The available information on use, mechanism of action, and pharmacokinetics is reviewed.

Résumé — Examen des médicaments pré-rendez-vous pour réduire la peur et l'anxiété chez les chiens et les chats lors des visites vétérinaires. Cette revue se concentre sur les médicaments pré-rendez-vous utilisés pour diminuer la peur et l'anxiété chez les chiens et les chats liées aux visites vétérinaires. Une recension de la littérature a révélé des données sur quatre médicaments de quatre classes de médicaments qui ont été utilisés pour diminuer la peur et l'anxiété situationnelles aiguës chez les chiens et les chats : la gabapentine, la trazodone, la dexmédétomidine transmucosale orale et l'alprazolam. Les informations disponibles sur l'utilisation, le mécanisme d'action et la pharmacocinétique sont passées en revue.

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Introduction

Dogs and cats show behavioral and physiologic indicators of stress at veterinary appointments and in veterinary hospitals (1–8). Fewer than half of dogs enter a practice calmly (2,3) and most show behavioral signs of stress in the waiting room (6). Cats have significantly lower signs of physiologic stress when examined at home than in a clinic (4,5). Only 26% of cats were calm upon arrival at a clinic and 60% exhibited ongoing distress upon return home (9). Behavioral medicine is an unmet need for veterinary staff, clients, and patients in most veterinary practices, posing a threat to the welfare and longevity of companion animals (7,10), for whom behavioral problems are the leading cause of abandonment and euthanasia (7).

Behavioral distress is not only harmful to a patient's mental well-being (11), but it can affect patient health, client compliance, diagnosis and treatment, and overall patient care (8). Pets that have negative experiences during veterinary visits are likely to be fearful and distressed during their next visit, further impeding delivery of care (8,12). Low stress environments and handling, alone, may not significantly lower anxiety, but the addition of behavioral medications may aid in mitigating anxiety and fear associated with veterinary care. Decreasing patient fear and anxiety improves veterinary visits for patients, clients, and the veterinary team, and decreases risk patients may pose to veterinary staff (11,12).

This review focuses on common medications that are used to facilitate less stressful veterinary visits. Peer-reviewed information was available for 4 medications from 4 medication classes for ameliorating acute situational fear and anxiety in dogs and cats: gabapentin, trazodone, oral transmucosal (OTM) dexmedetomidine, and alprazolam. All use is extra-label. The literature was reviewed for data on use, mechanism of action, and canine/feline pharmacokinetics (Table 1).

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Selected medications for use during veterinary appointments

Gabapentin

Gabapentin, a gabapentinoid, was developed as an anticonvulsant but has analgesic and anxiolytic effects (13,14), often with single dose administration before surgery (15). Gabapentin is anxiolytic in cats (16). Gabapentin is a controlled substance in some jurisdictions since it is often used illegally with opiates, greatly increasing the risk of opioid-related deaths.

How does this medication work? Gabapentin binds as a ligand to the $\alpha_2\delta$ subunit of voltage gate calcium channels, causing a decrease in the release of neurotransmitters such as the excitatory neurotransmitter, glutamate (17). Gabapentin

Table 1. Summary of uses, dosages, potential adverse effects and evidence available for 4 drugs used to reduce fear and anxiety in dogs and cats at veterinary visits.

Medication	Recommended uses for veterinary visits	Recommended dosage	Adverse effects	Reference
OTM gel dexmedetomidine (as Sileo®)	Fear of noises	Dogs: 4.65 μg/kg BW (125 μg/m^2) for a 20-kg dog up to 1 h before noise; repeatable every 2 h to 5 doses/d	Sedation Hypersalivation Vomiting	41
OTM injectable dexmedetomidine	Veterinary examinations	Dogs: 4.65 μg/kg BW (125 μg/m^2) for a 20-kg dog 20 min before transport/examination BSA (m^2) = 0.101 × (BW kg)$^{2/3}$	Sedation Hypersalivation Vomiting	43
	Sedation for short procedure	Cats: 20 μg/kg BW; BSA (m^2) = 0.1 × (BW kg)$^{2/3}$		38
	Sedate aggressive or anxious dogs	Dogs: mean dosage 32.6 μg/kg BW; range: 16.1 to 40 μg/kg BW		39
	Sedation for minor procedures and veterinary examination	Dogs: 20 μg/kg BW for procedure and sedation		40
Gabapentin	Lower stress during intradermal testing	Cats: 25 to 35.7 mg/kg BW	Sedation Ataxia Salivation Vomiting	21
	Decrease stress at transport	Cats: 100 mg/cat; 13.0 to 29.4 mg/kg BW, 90 min before transport/examination		19
	Sedate trapped, caged community cats for TNR	Cats: mean low dose group — 16.3 mg/kg BW; mean high dose group — 35.3 mg/kg BW; overall range: 9.2 to 47.6 mg/kg BW		20
	For veterinary visits	Dogs: 20+ mg/kg BW q1h, 2 to 3 d before visit, or the night before and morning of 2 to 3 h before visit		There are no studies on gabapentin as an anxiolytic in dogs.
Trazodone	For sedation for veterinary visits	Cats: 10.6 to 33.3 mg/kg BW, PO, 1 to 1.5 h before transport/examination (n = 6)	Sedation Vomiting, gagging, diarrhea Hypersalivation Paradoxical excitation Behavioral disinhibition Ataxia	32
	For sedation/handing facilitation for veterinary visits	Cats: 7.7 to 15.2 mg/kg BW PO, 1 to 1.5 h before transport/examination (n = 10)		33
	For confinement stress/sedation in dogs	Dogs: 3.5 to 10 mg/kg BW PO, q12h		34
	For behavioral signs of stress/distress in hospitalized dogs	Dogs: 4 mg PO, q12h to start; up to 8 to 10 mg/kg BW, PO, q8h; 90 min before hospitalization or procedure		35
	For anxiety associated with post-surgical confinement in dogs: ***NO EFFECT***	Dogs: 2.8 to 10.8 mg/kg BW, PO, q12h: ***NO EFFECT***		36
Alprazolam	Fear/panic prior to or caused by veterinary examination/transport	Cats: 0.0125 to 0.025 mg/kg BW, 30 to 60 min before appointment OR in an interventional manner when a cat becomes distressed	Sedation Ataxia Paradoxical excitement Possible disinhibition where aggression is inhibited	Cats: There are no studies on alprazolam as an anxiolytic in cats.
	Fear/panic prior to or caused by veterinary examination	Dogs: 0.02 to 0.04 mg/kg BW in an interventional manner when a dog becomes distressed OR given 30 to 60 min before appointment. Can put pill in the cheek, will dissolve.		45

BSA — body surface area; TNR — trap neuter release/return.

was developed as a chemical analogue to γ-aminobutyric acid (GABA) but does not affect GABAergic neuronal systems. Any effects on GABA are likely secondary to calcium channel effects, neuronal type, and regional responses (18).

Clinical studies. The use of gabapentin in cats and dogs is extra-label. Although gabapentin is increasingly used in the treatment of anxiety, there are no peer-reviewed efficacy or dose determination studies for this indication.

van Haaften et al (19) examined the effects of a single pre-appointment dose of gabapentin (100 mg/cat) on signs of stress in cats during transportation and veterinary examination. In a randomized, placebo-controlled, crossover study, 20 healthy pet cats [3.4 to 7.7 kg; 13.0 to 29.4 mg/kg body weight (BW)] with a history of fractious behavior or signs of stress during veterinary examination at 2 veterinary visits 1 wk apart, were investigated. Cats received 1 of 2 treatments (gabapentin or placebo) for the first visit and the second treatment for the second visit. Owners gave the capsule 90 min before placing the cat into the carrier. Owners and veterinarians scored the cats' compliance with examination and behavior using the 7-point cat stress score (CSS). Gabapentin significantly reduced perceived distress and increased compliance for the cats.

Gabapentin was evaluated as an anxiolytic for spay/neuter surgery in 53 community cats in a trap-neuter-return (TNR) program (20). Using a double-blinded, placebo-controlled design, cats were given a single dose of placebo, low dose gabapentin (50 mg/cat), or high dose gabapentin (100 mg/cat) in a 1-mL sugar solution. A blinded observer scored each cat for fear, sedation, respiratory rate, and facial injuries at the time of administration, 1, 2, 3, and 12 h after administration. Regardless of dose, gabapentin reduced fear compared to placebo. Cats in this study weighed 1.4 to 5.4 kg (mean: 3.4 kg in 50 mg/cat group; 3.0 kg in 100 mg/cat group), resulting in dosages of 9.2 to 24.4 mg/kg BW (mean: 16.3 mg/kg BW) and 23.1 to 47.6 mg/kg BW (mean: 35.3 mg/kg BW), respectively. The cats in the placebo group overlapped with the excitement range on the CSS and mg/kg BW given overlapped for the 2 dosages, blurring evaluation of CSS by group. Feral cats are considered fractious which may affect CSS scores in ways not relevant for companion cats.

In a randomized, single-blinded, crossover study of 16 companion cats, Hudec and Griffin (21) administered either gabapentin or no treatment, then the reverse, in a 2-visit study to determine any effect of gabapentin on intradermal testing, cortisol, and glucose. Gabapentin was administered in capsules using a pre-determined mg/kg BW range, with an increase of 25 mg of gabapentin for up to each additional kilogram of weight beyond 2 kg. The maximal dosage range was 25 to 35.7 mg/kg BW. There was no effect of gabapentin on cortisol or glucose, but gabapentin correlated with lower stress assessments, although sedation could not be ruled out.

At the time of writing, there are no published studies on the use of gabapentin for anxiety/fear in dogs.

Pharmacokinetics. Intravenous (IV) (4 mg/kg BW) and oral (10 mg/kg BW) gabapentin pharmacokinetics were compared in a randomized, crossover study in 6 female adult shorthair cats (16). Disposition was best described by a 1-compartment model for oral administration, but a 3-compartment model for IV administration. The terminal half-life for IV gabapentin was 170 ± 21 min (range: 151 to 198 min) and the $t_{1/2}$ for orally administered gabapentin was 177 ± 25 min (range: 151 to 211 min). T_{max} for orally administered gabapentin was 100 ± 22 min (range: 58 to 175 min). Based on the effective human plasma concentrations for analgesia in neuropathic pain and feline pharmacokinetics, the recommended dose was 3 mg/kg BW, PO, q6h.

In a non-randomized, block design, single dosages of 10 and 20 mg/kg BW of gabapentin were given to 6 healthy greyhound dogs, 1.5 to 3 y old, to determine pharmacokinetic parameters (22). Mean dosages administered were 10.2 mg/kg BW (range: 9.1 to 12.0 mg/kg BW) and 20.5 mg/kg BW (range: 18.2 to 24 mg/kg BW), respectively. C_{max} occurred at 1.3 and 1.5 h, and the terminal half-lives were 3.3 and 3.4 h, respectively for each dose group. These findings were similar to the 2.9 h C_{max} reported for intravenous dosing in dogs at 25 mg/kg BW per day for 14 d and 100 mg/kg BW per day for 28 d (n = 2 beagle dogs) (23). The $t_{1/2}$ of oral gabapentin was 3 to 4 h in dogs, 2 to 3 h in rats and 5 to 6 h in humans (24). Rapid absorption and elimination suggest the need for frequent dosing to maintain targeted plasma concentrations (24). Dogs, unlike cats and humans, metabolize about 34% of gabapentin to N-methyl-gabapentin (23,24).

Rhee et al (25) compared a gabapentin 600 mg single dose sustained release formulation with a single dose immediate release formulation in 4 fasted beagle dogs, 10 to 12 kg (50 to 60 mg/kg BW). There were concerns with dissolution and absorption of the sustained release tablet, but the plasma concentration *versus* time curves were similar for both formulations with fully overlapping error bars. For the immediate release formulation, used in all studies reported here, time to reach C_{max} (T_{max}) was 2.0 ± 0.0 h and $t_{1/2}$ was 3.2 ± 0.2 h.

Because gabapentin is excreted through the urine, renal tubule impairment can concentrate gabapentin in renal tubules (23), and dosages may need to be decreased in animals with renal disease.

Recommended use. The range of gabapentin dosages reported (19,20) is large: 13.0 to 29.4 mg/kg BW for companion cats and 9.3 to 71.4 mg/kg BW for community cats. We lack clinical and dose determination studies, but based on available data, 3 to 10 mg/kg BW may be a reasonable dose for cats. Reported adverse effects include sedation and ataxia (16,19), and vomiting and hypersalivation (20,21). Gabapentin is given by capsule or compounded in liquid. Dogs should not be given the commercially available oral gabapentin solution as it contains xylitol.

Although there are multiple pharmacokinetic studies in dogs and gabapentin is widely used by specialists for fear and anxiety at the equivalent dose recommended for pain (20 mg/kg BW) or greater (26), there are no published clinical studies on the use of gabapentin to decrease situational anxiety in dogs. Such studies are needed. Given the studies in cats and anecdotal specialist usage (26), the anxiolytic dose of gabapentin may be higher than the analgesic dose, as in humans (14,15), but this clinical impression requires testing.

Based on pharmacokinetics, gabapentin may be given to dogs and cats to prevent fear or anxiety at veterinary visits at least 90 min before the visit. Some benefit has been anecdotally reported for some dogs of starting the gabapentin the evening before and the day of the veterinary visit, with the final dose coming 90 min before the appointment (26). Based on pharmacokinetic data, to overcome troughs in plasma values, dosing should be at least every 8 h (22–24).

Trazodone

Trazodone is a serotonin antagonist and reuptake inhibitor (SARI) that is commonly used to mildly sedate cats and dogs for veterinary care. It has also been used to prevent distress, anxiety, and hyper-arousal during transport and during examinations (27). In human psychiatry, trazodone's primary use is as an hypnotic in insomnia and disordered sleep, including that occurring with depression and post-traumatic stress disorder, because it decreases sleep latency and increases sleep duration (28).

How does trazodone work? Trazodone acts as an antagonist, primarily blocking the serotonin 2A (5-HT2A) and 2C (5-HT2C) receptors. The 5-HT2A and 2C receptors affect cognition and movement, respectively, with both affecting sleep, in a dose-dependent manner. Considered a multi-functional medication (29), trazodone only functions as an antidepressant in humans at a dose that blocks the serotonin transporter (SERT). The antidepressant/SERT blocking dose in humans is 10- to 50-fold higher than that necessary to block 5-HT2A receptors. Similar data are unavailable for dogs and cats. Trazodone's intermediate metabolite, meta-chloro-phenyl piperazine (mCPP), functions as an agonist, and has high affinity for several serotonin receptors, with the 5-HT2C receptor preferred. Trazodone has more minor reuptake inhibition effects at other presynaptic serotonin receptors, acts as a 5-HT1A agonist stimulating release of serotonin, and is a potent histamine 1A and α-1 adrenergic antagonist.

Concurrent use with selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs) should be monitored closely due to an enhanced risk of serotonin syndrome. Concurrent use with monoamine oxidase inhibitors is contraindicated since the shared neurochemical synthesis pathways enhance risk for serotonin syndrome. Signs of serotonin syndrome include tachycardia, hypertension (particularly in cats) (30), altered mental state or behavioral changes, diarrhea, hyperthermia, shivering, tremors, and seizures (12). Death ensues without treatment. Most reports of serotonin syndrome in companion animals are iatrogenic (high or incorrect dosages) or due to accidental ingestion of bottles of medication (12). Heart rate can be monitored since increased heart rate (> 30% of baseline) may be an early indication of excessive serotonin and the activation that follows (12). Heart rates > 150 beats/min are reported for dogs with serotonin syndrome due to overdose associated with accidental ingestion. Hepatotoxicity has been documented in 1 dog treated with trazodone 4 mg/kg BW, q12 to 24h (31).

Clinical studies. Trazodone is used extra-label in dogs and cats, and has undergone no dose determination studies.

In a randomized study (n = 6 cats), evaluation was as a sedative for transport and examination (32). Each cat served as its own control and was given a single dose of each of 4 treatments over 4 wk: placebo and 1 dose each of 50, 75, and 100 mg trazodone (10.6 to 16.7 mg/kg BW, 16.0 to 25 mg/kg BW, and 21.3 to 33.3 mg/kg BW, respectively). Sedation was measured by accelerometry, the CSS, and behavioral measures. Peak sedation occurred 2.5 h after the 100 mg dose, although the range across this small group of cats was wide, extending to 3 h. CSS did not differ at any time point between placebo and treatment groups, suggesting that the clinical effect was one of true sedation, not anxiolysis. The largest proportional sedative effect occurred after the 50 mg dose, suggesting that it may be sufficient for transport and clinical evaluation.

Stevens et al (32) compared a 50 mg trazodone dose (7.7 to 15.2 mg/kg BW) to a placebo in a single-blinded, randomized study with 10 client-owned cats with a history of distress related to transport and/or examination. Cats were medicated 90 min before travel and examination. Clients used the CSS and a tool to score tractability before, during, and after transport and examination. Veterinarians evaluated the cats before, during, and after examination. Cats given trazodone exhibited less stress before transport (P = 0.02), in the waiting room (P = 0.02), during veterinary examination (P = 0.04), and after (P = 0.008) the examination. This study did not differentiate between sedation and anxiety relief, nor did it evaluate post-examination recovery. The difference between anxiety relief and sedation may not matter to clients or patients since the cat does not experience distress, but clients should know about it and that recovery period from sedation is variable.

In an open-label, prospective study of 36 dogs, Gruen et al (33) evaluated calmness in dogs given trazodone (~3.5 mg/kg BW, PO, q12h) in combination with tramadol (4 to 6 mg/kg BW, PO, q8–12h) for pain management during post-surgical confinement. After 3 d, the tramadol, which also affects serotonin, was stopped and trazodone was increased to 7 mg/kg BW, PO, q12h and maintained for 4 wk. Clients could increase trazodone to 7 to 10 mg/kg BW, PO, q8h. Clients evaluated their dogs for confinement tolerance, calmness/hyperactivity level, and responses to specific provocative situations, before surgery and at 1, 2, 3, and 4 wk and at the post-surgical evaluation (8 to 12 wk) using an electronic survey. Clients reported that trazodone enhanced confinement tolerance and calmness, that the onset of action was 35 to 45 min, and that effects lasted at least 4 h. Almost all clients (32/36) thought that trazodone was moderately or extremely helpful for calming the dog.

Trazodone has been evaluated for use in management of anxiety in hospitalized dogs (34). Hospitalized dogs displaying any behavioral signs of stress or distress (n = 59) were administered trazodone at 4 mg/kg BW, PO, q12h, with the dose or frequency increased to 10 to 12 mg/kg BW or to every 8 h when needed for desired calming and anxiolytic effects (not to exceed 300 mg/dose or 600 mg/24 h). In this observational study, dogs were matched with an untreated nearby dog (n = 58) to control for environmental effects. Dogs were evaluated at 45- and 90-minute post-treatment for 22 stress-related behaviors. Lip licking, panting, and whining decreased significantly in the dogs receiving trazodone. Sedation and other functional and

physiological parameters were not measured. The results suggest that trazodone be given 90 min before the examination.

A randomized, placebo-controlled, double-blinded study (35) tested the efficacy of trazodone to specifically relieve anxiety — distinguished from sedation — in the confinement period after orthopedic surgery. This study compared 14 dogs treated with trazodone to 15 dogs treated with a placebo over 4 wk. The dosage range intended was 5 to 7 mg/kg BW, PO, q12h. Because clients were permitted to increase or decrease the amount of the tablet they were given depending on response, the actual final dose used was 5.6 to 21.6 mg/kg BW per day (mean ± standard error = 15.13 ± 1.6 mg/kg BW per day) or 2.8 to 10.8 mg/kg BW, PO, q12h. This study is the only fully randomized, placebo-controlled, blinded study to date and there were no statistically significant differences between the treatment and placebo groups in any of the behavioral categories. This outcome should not be surprising. Trazodone is best used in humans for its mild-to-moderate sedation and hypnotic effects, as explained by its receptor profile (28). It is not a first-line anti-anxiety agent.

Pharmacokinetics. In a randomized, controlled, crossover study, 6 beagle dogs were given a single dose of 100 mg (8.26 ± 0.26 mg/kg BW) of trazodone orally and 8 mg/kg BW, IV (36). Neither mean nor systolic arterial blood pressure was correlated with trazodone concentration, route or time, but all dogs developed transient tachycardia following IV administration and 3/6 dogs became uncharacteristically aggressive within 5 min after IV administration.

The T_{max} for oral trazodone was 445 ± 271 min (7.4 ± 4.5 h), with peak plasma concentrations reached in 8 to 12 h for 5/6 beagles tested and 30 min for 1 dog (36). Plasma concentrations of trazodone varied by dog: for 2/6 dogs, plasma concentrations were maintained at > 130 ng/mL for 4 h, for 2/6 dogs for 14 h, for 1/6 dogs for 10 h, and for 1/6 dogs for 20 h.

Following oral administration, the elimination half-life was 166 ± 47 min, comparable to the 169 ± 53 min reported for IV dosing.

Bioavailability following oral dosing was 84.6 ± 13.2%, higher than that reported for humans. Dogs in this study had a C_{max} of 1.3 ± 0.5 g/mL when given 8 mg/kg BW, compared to humans, who had a C_{max} of 1.47 ± 0.16 g/mL when given 100 mg trazodone (1.3 to 2 mg/kg BW). This finding suggests the need for a full pharmacokinetic and dose determination study for use of oral trazodone since it suggests that one must give 4 times the dose used in humans to dogs to obtain similar blood concentrations. Because of the multi-functional nature of trazodone (29), higher dosages affect primarily the 5-HT2C receptor. This receptor is the target for mCPP, which is a potent serotonergic agonist. In humans, ~20% of the parent compound is metabolized to metabolically active mCPP. Such data are lacking for dogs and CYP 450 activity varies across species and genotype (12). mCPP can be anxiogenic: panic, anxiety, dysphoria, and psychosis are reported in humans. Similar effects have been reported anecdotally in dogs receiving high dosages of oral trazodone.

Recommended use. Studies evaluating medications are inconsistent in their use of terminology and fail to differentiate between calming *versus* anti-anxiety *versus* sedative effects. These differences matter. This lack of clarity complicates recommendations for use. For licensed medications, regulatory agencies require that anxiolytic and sedative effects are distinguishable and that the anxiolytic effects occur without overt sedation. These distinguishing data are lacking for most of the published studies involving trazodone.

Wide dosage ranges have been reported for trazodone in both cats and dogs. No source stated a recommended dose, although Gilbert-Gregory et al (34) recommended a maximum of 300 mg/dose or 600 mg/24 h in dogs.

The differences between sedation and anxiolysis should be explained to clients so that they can understand the benefits of both and thereby formulate realistic expectations.

For mild-moderate sedation in dogs that are hospitalized or undergoing veterinary examination, the cumulative dosage range reported is 3.5 to 12 mg/kg BW, PO up to q8h (34,35). Administration should be 90 min before the procedure for one-time use. For cats undergoing veterinary examination, the cumulative dosage range is 7.7 to 33.3 mg/kg BW once, 90 min before the procedure (32,33,37).

Oral transmucosal (OTM) dexmedetomidine

Injectable dexmedetomidine is widely used for sedation in dogs due to its reversible nature and favorable cardiovascular and respiratory risk profile. Because the oral cavity has a rich vascular supply, the injectable formulation has been used by the OTM route in clinical settings and a specific low-dose OTM gel, (Sileo; Zoetis, Parsippany, New Jersey, USA) has been developed and approved in the European Union and the United States for dogs that fear noises. Other uses are extra-label.

How does dexmedetomidine work? Dexmedetomidine, an enantiomer of medetomidine, is a centrally acting α-2-adrenergic receptor agonist which has anxiolytic, sedative, and hypnotic actions. These actions are mediated through inhibiting locus coeruleus (LC) firing. Neurons from the LC project to the limbic system, providing noradrenaline for the forebrain. The LC modulates sympathetic tone, vigilance, and attention. Inhibiting noradrenaline release from the LC decreases arousal by reducing the stimulation of the hypothalamic pituitary axis sympathetic outflow, decreasing fear and anxiety (26).

Clinical studies. Use of this medication in cats is extra-label, as are some canine usages.

In a block randomization study comparing injectable *versus* oral buprenorphine (20 μg/kg BW) combined with dexmedetomidine (20 μg/kg BW) to facilitate catheter insertion in cats, OTM injectable dexmedetomidine allowed for easier catheter placement than did injectable dexmedetomidine, and produced less sedation (38). Benefits of OTM administration were decreased aversion for cats to the administration route and decreased risk of accidental needle sticks to humans (38). Differences in sedation associated with route may be due to decreased bioavailability associated with salivation, vomiting, and swallowing (which inactivates the compound). Less compound crossed the mucous membranes into the bloodstream than occurred with injection. When salivation or vomiting was minimal, oral and injectable administration had similar sedative effects (38).

Injectable dexmedetomidine as an OTM solution was used to sedate 4 aggressive or anxious dogs (39). The range of dog body weights was 21.8 to 38.7 kg. The dosage ranges for sedation for this weight range would have been 14.5 to 18 μg/kg BW (250 μg/m^2) and 11 to 13.4 μg/kg BW (500 μg/m^2) for IM and IV administration, respectively. The mean dosage for the OTM administration was 32.6 μg/kg BW (range: 16.1 to 40 μg/kg BW), 2 to 3 times the upper range for IM and IV administration. Three of the 4 dogs had a sedation score of at least 12 within 13 to 34 min.

A blinded, single observer, randomized, crossover study (40) compared IV dexmedetomidine (5 μg/kg BW) with OTM administration (20 μg/kg BW) of injectable dexmedetomidine in dogs for short procedures. The OTM dexmedetomidine resulted in a similar degree of sedation and prolonged duration of action, compared with results for IV administration, despite relatively low bioavailability.

Oral transmucosal dexmedetomidine gel (Sileo; Zoetis) was tested for alleviation of fear of fireworks noise in a randomized, double-blinded, placebo-controlled clinical study (41). With sub-sedative doses of 125 μg/m^2 (~4.65 μg/kg BW in a 20 kg dog), dogs in the treatment group were statistically significantly less distressed and fearful than dogs in the placebo group, with an excellent or good effect reported for 72% of the dogs treated with dexmedetomidine than 37% of those treated with a placebo. Dogs in the dexmedetomidine treatment groups expressed significantly fewer signs of fear and anxiety (panting, trembling, pacing, elimination) while listening to fireworks. Based on a functional alertness assessment scale, $>$ 85% of the dogs in the treatment groups remained fully functional throughout the event. The most severe effect reported was emesis (41).

A blinded, placebo-controlled, crossover study involving 40 dogs tested with OTM dexmedetomidine gel used off-label at the labeled dose (125 μg/m^2) reduced fear and anxiety during veterinary visits when administered at home by owners before the visit (42). Use of OTM dexmedetomidine gel at the labeled dose decreased the likelihood that the dogs would exhibit stress/fear vocalization (whining, yelping, grumbling) ($P < 0.01$), avoidance behaviors (oriented toward the door, attempting to exit the room, trying to jump from the table) ($P < 0.01$), and the group of behaviors including panting, trembling, urination, defecation ($P < 0.016$) during the physical examination, although neither the veterinarian nor the clients thought that the dogs were easier to examine.

Pharmacokinetics. Bioavailability of oral dexmedetomidine is poor due to extensive first-pass metabolism, but when administered *via* the oral mucosa, enhanced bioavailability resulted from absorption in the oral cavity and the avoidance of first-pass metabolism in the liver. The oromucosal mean bioavailability of OTM dexmedetomidine gel was 28% (43).

Dexmedetomidine is biotransformed and has a half-life in dogs of 0.5 to 3 h after OTM administration. More than 98% of it undergoes hepatic metabolism and fecal elimination. The maximum concentration occurs ~0.6 h after intramuscular or oromucosal administration (43). The onset of action is approximately 20 min (43).

When comparing OTM injectable dexmedetomidine with IV administration, C_{max} was 3.8 ± 1.3 ng/mL) for OTM administration, and T_{max} was 73 ± 33 min. C_{max} for IV administration was 18.6 ± 3.3 ng/mL and T_{max} was 1.5 ± 0.6 min. The mean terminal-phase $t_{1/2}$ was 152 ± 146 min for OTM administration and 36.6 min for IV administration. Bioavailablity for the oral administration was 11.2 ± 4.5%, 40% of that reported for the OTM dexmedetomidine gel (43).

Peak sedation scores did not differ significantly between routes of administration, but time to peak sedation score was lower for IV administration [10 min (range: 2 to 45 min) *versus* 38 min (range: 30 to 60 min)] and time to return to baseline was shorter (240 *versus* 480 min for OTM).

Recommended use. The fast onset of action (20 min) and rapid T_{max} (30 min) for the OTM gel suggests that it may help anxious dogs in a clinical setting. Blocking the arousal phase of distress, fear, and anxiety by blocking an noradrenaline pulse from the locus coeruleus has applications for anticipatory fear of and distress caused by veterinary visits (42), and for other situations involving arousal and acute anxiety including departures for dogs with separation anxiety and approaches from other dogs or humans for dogs which are fearful.

Oral transmucsoal dexmedetomidine gel is dosed at 125 μg/m^2 body surface area (each mL = 0.1 mg dexmedetomidine; 3 mL per syringe; 1 dispensing dot = 0.25 mL/25 μg) (43). For those lacking access to the licensed product, 25 to 40 μg/kg BW of the injectable dexmedetomidine has been given OTM (39). The anti-anxiety dose is lower than the sedative dose, but not established for OTM injectable dexmedetomidine.

In a survey of 1225 clients with dogs that reacted to fireworks, Riemer (44) reported that of all the treatments used, 74% of those using OTM dexmedetomidine gel said it was effective.

Alprazolam

Alprazolam is a benzodiazepine, a class of medications typically used in pre-anesthetic and sedation protocols and for the treatment of anxiety, fears, phobia, and panic in cats and dogs, and in humans. Benzodiazepines have anxiolytic, panicolytic, relaxing, antiepileptic, and muscle relaxing effects in humans and in cats and dogs, and a label for use for specific anxiety in humans. The exact mechanism of these effects is undescribed and dependent on dosage and individual response.

How does alprazolam work? Benzodiazepines bind to specific sites on the gamma-aminobutyric acid A ($GABA_A$) receptors, increasing flow of chloride ions into the neuron, enhancing the inhibitory effects of GABAergic neurons. Alprazolam, a triazolobenzodiazepine, is commonly used for behavior due to the rapid onset, anxiolytic, and truly panicolytic properties (12,45). Benzodiazepines have amnesic effects at clinically relevant doses, which is useful for sedation protocols and in animals experiencing profound fear or phobias (12,26,45). The muscle relaxation caused by benzodiazepines is independent of sedation and may help with patient fear and anxiety, as fearful animals typically have increased muscle tone (12,26,45).

Clinical studies. Use of this medication is extra-label.

Crowell-Davis et al (46) conducted an open-label trial evaluating clomipramine, alprazolam, and behavior modification for

the treatment of storm phobia in dogs. Clomipramine (2 mg/kg BW) was given every 12 h. Alprazolam (0.02 mg/kg BW) was given 1 h before the expected storm and every 4 h as needed thereafter. Of the 32 dogs that completed the study, 30 were deemed by the clients and clinicians to have improved. When baseline scores were compared to those post-treatment 4 mo later, the signs of storm-specific anxiety that significantly decreased following administration of alprazolam were panting, pacing, trembling, remaining near the caregiver, hiding, excessive salivation, destructiveness, excessive vocalization, self-trauma, and inappropriate elimination. Improvement was best demonstrated during storms involving rain, thunder, and lightning, compared to those involving only rain.

Pharmacokinetics. The pharmacokinetics of alprazolam have not been described in cats and dogs. In human medicine, alprazolam is considered an intermediate-acting benzodiazepine with peak plasma concentration occurring 1 to 2 h after ingestion and mean plasma elimination $t_{1/2}$ of 11.2 h (range: 6.3 to 26.9 h).

Recommended use. Alprazolam may have a role in reducing anxiety and fear in patients during veterinary visits, although there are few reports in the literature (12). Use may also be interventional when a dog becomes distressed or panicked while undergoing veterinary care (12). This panicolytic effect has been observed in humans (45) and in cats and dogs (12). In cats, alprazolam has been primarily used to prevent fear and anxiety associated with travel and handling during examinations and procedures, but given the role that olfaction plays in contributing to feline reactivity, alprazolam may also be considered for use in cats returning from the hospital to a multi-cat household because of the altered olfactory social environment (12,26).

Alprazolam can be used interventionally if a patient becomes severely distressed or fearful during an appointment, and preventatively 30 to 60 min before the appointment to help relieve fear and anxiety and/or over 2 to 3 d before the appointment to reduce anticipatory anxiety (11).

The starting range is 0.02 to 0.04 mg/kg BW (44), but dosages as high as 0.1 mg/kg BW have been reported (12,47). In cats, the published dose range is 0.0125 to 0.025 mg/kg BW/0.125 to 1 mg/cat (48). There are no dose determination studies for alprazolam in cats and dogs.

The major adverse effect reported with use of benzodiazepines is sedation. Alprazolam is less sedative than diazepam and most adverse effects of benzodiazepines, including sedation and ataxia, are dose-dependent (12,49). Paradoxical excitement has been reported in cats and dogs, as has disinhibition of previously inhibited behavior (e.g., aggression) (12,46,49). Benzodiazepines are well-known for highly individually variable responses so recommendations are to start at a low dose and have clients give the first dose or two when they are at home to monitor their pet for any adverse reactions. Extremely rare, long-lasting adverse reactions or those posing a risk to the patient can be reversed with IV flumazenil.

Riemer (44) reported that 90% of 1225 owners surveyed who used alprazolam, alone, on an "as needed" basis reported it effective at reducing signs of fear in their dogs during fireworks. Using alprazolam as needed and clomipramine twice daily was effective for treating dogs with storm phobias in a prospective trial (46). Alprazolam has also been used successfully as an adjunctive therapy for separation anxiety and as a preventative or interventional treatment for noise phobias (12).

Alprazolam may facilitate less stressful and fearful visits to veterinary hospitals if given 1 h before the anticipated appointment. Due to the amnesic, anxiolytic, and panicolytic effects, alprazolam may be useful interventionally when patients become profoundly distressed during an appointment.

The concern for abuse potential

All benzodiazepines are abusable by humans and are controlled substances. Gabapentin is increasingly listed as a controlled substance due to its concomitant use with opioids in addiction and the subsequent increased risk of fatal overdose.

Not all medications belong in all client households. In addition to asking clients if there is anyone in the household or who visits the household who has a substance abuse issue, risk can be minimized by prescribing small amounts of medications that can only be renewed by talking with the veterinarian and with evidence of a beneficial effect (video, completed patient logs). Medication must be secured within the household, and clients should be cautioned not to advertise its presence. Re-examinations present an opportunity to review risks and benefits. All medications can be dispensed using a schedule and oversight that make abuse both difficult and more obvious.

Conclusion

This review focuses on behavioral medications for preventing or treating anxiety, stress reactions, and distress that occur in the context of veterinary care. Covariates of anxiety/distress before/during veterinary care include increased client stress, patient panic, enhanced patient aggression and oppositional responsiveness, and increased risk to the veterinary staff (6,7,9,11). Clients whose dogs and cats are fearful are less likely to use veterinary care except in an emergency, and worry about their companion's welfare when they do seek care (6,9,50).

Of the 4 medications for which there was published information, 3 are not licensed for use in dogs or cats. Except for the licensed OTM dexmedetomidine, pharmacokinetic data are sparse and dose determination studies are lacking. This pattern is problematic. The existence and publication of these data would provide veterinarians with a greater comfort level in dispensing the medications discussed.

There are no published clinical studies on the use of gabapentin to address anxiety in dogs in any situation. Although there are some data on pharmacokinetics of gabapentin in dogs that suggest that the dosages discussed here are reasonable, dose-determination and efficacy studies are needed.

Trazodone needs to be more closely monitored in terms of dosages, systemic activating effects of serotonin, especially if TCAs or SSRIs are given concomitantly, or if high dosages are used, and other adverse events (31). Trazodone may be best used for its hypnotic properties for dogs in hospital settings in which sedation of some level is desired; this has been the focus of most of the published work (33,34). There are no dose determination studies for trazodone.

Oral transmucosal dexmedetomidine gel can be conveniently used to decrease anxiety and prevent distress (40,41). Oral transmucosal injectable dexmedetomidine may also be useful for decreasing anxiety and preventing stress at low dosage levels, but published studies are lacking. There are no dose determination studies for injectable dexmedetomidine used OTM as either a sedative or anxiolytic agent. Alprazolam is commonly used "as needed" for anxiety, fears, and phobias (44). There are no dose determination studies for alprazolam.

Behavioral medicine uses a multifactorial approach to treatment (12,47), with treatment plans tailored to a dog or cat's individual needs (37). Behavioral medications stimulate translational changes involved in learning and so enhance and speed the effects of behavior modification (12). Combined with changes in handling, difficulty, stress, and distress involved in veterinary visits can be minimized for everyone (7).

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