ON THE USE OF TRAZODONE IN VETERINARY MEDICINE

Dragos CRICLEVIȚ[1], Gheorghe SOLCAN[2], Alin CIOBÎCĂ[3], Luminita Diana HRITCU[4]

Abstract. *Trazodone is the main anxiolytic used in veterinary medicine because it reduces physiological stress in cats and dogs which can be significant. In this case, the animals are prone to illness due to the body's decreased immunity. Four drugs from four different classes can be used to relieve acute situational fear and anxiety in dogs and cats, including trazodone, gabapentin, alprazolam and dexmedetomidine taken orally. Doses differ according to behavioral and medical conditions. In anxiety the dose in dogs is: 1.9-16.5 mg/kg q24h for daily medication or 1.7-19.5 mg/kg q24h combined daily and as needed administration or 2.2-14 mg/kg q24h (as needed administration) for general anxiety 4-12 mg/kg q24h for 1.5 h before a veterinary visit. In cats the dose is 7.7-15.2 mg/kg q 24h for 1-1.5h before a visit to the veterinarian. Preoperatively and postoperatively in cats no dose studies have been reported. In dogs preoperatively 5-7 mg/kg administered 2 h before surgery combined with an opioid (Tramadol, Bupaq/Alvegesic) as premedication for anesthesia and orthopedic surgery. Postoperatively give 1-3.5 mg kg/kg in combination with tramadol for 3 days and then 7 mg kg-1q 12 h or 7-10 mg kg-1q 8 h as needed for 4-12 weeks for orthopaedic surgery. Trazodone has a much higher risk of adverse reactions in geriatric patients including: callus, vomiting, colitis, colitis, sedation, increased appetite, paradoxical excitement hypersalivation.*

Keywords: Trazodone**,** behavioral stress, anxiety, preoperative, postoperative

DOI 10.56082/annalsarsciagr.2024.2.70

1. Introduction

For pets, visits to veterinary surgeries or veterinary hospitals cause significant stress which predisposes them to illness due to decreased immunity. If patients come to the clinic because of wounds or other various pathologies, anxiety prolongs their healing. Being panicked, dogs and cats show behavioral disturbances such as nervous excitation or nervous inhibition (due to too much stress, cats can also go into cardio respiratory arrest). For example, they are very difficult to contain, attacking both owner and doctor by biting, scratching, becoming reactive. Some of the patients even

[1]PhD Student, Med. Vet., University of "Life Sciences Ion Ionescu de la Brad", Iași, Department of Clinical Medicine, Faculty of Veterinary Medicine, România (e-mail: criclevitdragos@yahoo.com)
[2]Prof. Phd. Gheorghe Solcan, University of "Life Sciences Ion Ionescu de la Brad", Iași, România, Faculty of Veterinary Medicine, (e-mail: gsolcan@yahoo.com)
[3]Assoc. Prof. PhD, University of "Life Sciences Ion Ionescu de la Brad", Iași, România, (E-mail: lumidih@yahoo.com)
[4]Researcher I PhD. Habil. University of "Life Sciences Ion Ionescu de la Brad", Iași, România Department of Biology, Faculty of Biology, Iași, România, (E-mail: alin.ciobica@uaic.ro)

run away from their owners and doctors, making them very hard to find in the end. Because animals are very aggressive, veterinarians have to face new challenges, including doing their best to reduce their nervous disorders and explaining to them that frequent visits to the vet itself causes panic, which is physiological. Some keepers are very understanding, while others blame us doctors, saying that they are generally very sociable, calm. Because of this, reticent animals are a real mental barrier that needs to be managed very well, as they are nowadays considered "family members" [12].

Veterinary medicine is constantly evolving, and behavioral problems in animals are becoming easier to manage. These disorders include generalized anxiety, separation anxiety and phobias of specific stimuli, including thunderstorms, fireworks and loud noises. These states of fear affect their welfare and have a negative impact on the bond between humans and animals, leading to their abandonment in animal shelters [8].

Of all these, trazodone is the most sought-after anxiolytic by veterinarians as well as humans, and the commercial product is Trittico. It is a triazolopyridine derivative and is part of the phenylpyrazine class of drugs. The intermediate metabolite of trazodone, meta-chloro-phenyl piperazine (mCPP), functions as an agonist and has high affinity for several serotonin receptors, with the 5-HT2C receptor being preferred. At the same time it is also a histamine 1A and adrenergic a-1 antagonist [6].

This anxiolytic increases serotonin concentrations by reducing the inhibitory tone of γ-aminobutyric acid neurotransmitters in the cerebral cortex, resulting in it being an anti-panic drug. Its main pharmacologic mechanism is that it is a serotonin 2A receptor antagonist and has a secondary mechanism of inhibition of brain neurotransmitter reuptake inhibition being classified as SARI. Trazodone is commonly used because it rarely presents side effects including: headache, vomiting, ataxia, ataxia, astaxia, priapism [8]. If used concomitantly with selective serotonin reuptake inhibitors (SSRIs) including: Citalopram, Escitalopram, Fluoxetine, etc. or with tricyclic antidepressants (TCA): Imipramine, Amitriptyline, Doxepin should be frequently supervised because there is a major risk of serotonin syndrome. Within the same symptom we have the following symptoms: hyperthermia, diarrhea, tremors, hypertension being common in cats, tachycardia, behavioral changes but especially seizures [6].

2. Materials and Methods

1 Materials used in trazodone studies

a. Active substance - Trazodone

Trazodone is a member of a class of antidepressants called serotonin reuptake inhibitors and 5-HT2A receptor antagonists (SARIs). The chemical formula of

trazodone is C19H22ClN5O and it is available in various pharmaceutical forms, including tablets and injectable solutions.

b. Pharmaceutical preparations

Trazodone is available in various dosage strengths, usually as tablets (50 mg, 100 mg, 150 mg) or oral suspensions. Of all these, trazodone is the most sought-after anxiolytic by veterinarians as well as humans, and the commercial product is Trittico. In clinical and laboratory studies, standardized forms of the drug are used, often prepared in tablet form to allow precise dosage administration.

c. Study subjects

Animal models: In preclinical investigations, mice or rats are usually used to evaluate the effects of trazodone on behavior, metabolism, and other physiological parameters. Stress-induced depression models are also used to study the mechanisms of drug action.

Thus the most common combination with low side effects in post-surgical interventions is tramadol-trazodone and antimicrobials. In dogs on the day of surgery, trazodone 3.5 mg/kg per os at 12h and tramadol 4-6 mg/kg per os at 8-12 h for pain management was administered. The median onset of action of trazodone was 31-45 minutes. Tramadol medication was discontinued after 3 days, and the dose of trazodone was increased (7mg/kg, PO, at 12 h) and maintained for at least 4 weeks. Trazodone was administered for 8-12 weeks after surgery and remarkable results were observed in calming the animals in isolation and thus reducing stress. No life-threatening side effects were observed during the course of the main anxiolytic medication. These included diarrhea, constipation, thirst, restlessness, drowsiness. It was also very well tolerated in combination with non-steroidal anti-inflammatory drugs (Meloxicam, Rheumocam, Loxicom). Trazodone in cats after post-surgical interventions no studies have been published.

Another study was done on a larger group of dogs that were divided into 2 subgroups: half that received trazodone and half that did not. Between these two subgroups there were no significant differences in: age, weight, sex, mixed-breed/pure-bred dogs ratio, time interval between the two behavioral observations. Anxiolytic was administered throughout the hospitalization (over 12 weeks) based on stress-related behavior. The starting dose is 3.5 mg/kg every 12h and will be given in food always. It will not be given before surgery because they are then not allowed to eat and drink water [9].

Trazodone was given to dogs showing signs of stress, anxiety, aggression. Behavioral signs of stress included intensive lip licking, frequent barking, teeth grinding, mydriasis, ears laid back, trembling. Two observations were made after administration: one more than 45 minutes and the second approximately 90

minutes after trazodone administration. There was no reduction in signs of stress in the control group, and there was a reduction in specific signs of stress in the medicated group [9].

Trazodone was not given alone but in combination with other medications including: Nonsteroidal anti-inflammatory drugs (tramadol, meloxicam, carprofen), gastric protectants (controloc, omeprazole, sucralfate), opioids (bupremorphine, butofarnol), systemic antimicrobials (metronidazole, cephalexin, amoxicillin-clavulanic acid, enrofloxacin, ampicillin-sodium-sulbactam, marbofloxacin or amikacin sulfate), corticosteroids (prednisolone, dexamethasone), antiemetics (ondansetron hydrochloride, maropitant citrate, metoclopramide hydrochloride). Of the total in the group, most were given a combination of trazodone but also non-steroidal anti-inflammatory drugs and if they are to be given for a long period of time, gastric protectants are also recommended. The owners of the dogs were satisfied with this anxiolytic which gave satisfactory results alone/combination with other medications [9].

A study was done on 41 dogs that underwent surgery for: stabilization of dislocated patella, repair of cruciate ligament tear, repair of pelvic fractures and removal of fragmented coronoid process. Of a total of 41 dogs, 6 were withdrawn due to owners not complying with the survey and no adverse reactions were observed [9].

This anxiolytic will be administered from the start for at least 4weeks twice/day per os. During the first 3 days postsurgery, owners were instructed to administer trazodone at an initiation dose (half the standard dose, approximately 3.5 mg/kg, P.O. at 12 h), as well as the analgesic tramadold (4 to 6 mg/kg at 8 to 12 h, being a drug with serotonergic activity. From 3 days after the intervention the opioid dose was discontinued and at the same time the dose of trazodone will be 7 mg/kg at 12h per os. The duration of action of trazodone is a maximum of 4 h with a latency to the effect of trazodone between 45-90 min after administration [2].

No adverse reactions were observed in the dogs studied (Table 1). The exception is 2 dogs in which the owners administered a double dose of trazodone than prescribed (20 mg/kg), and another dog was given tramadol for more than 3 days concomitantly with anxiolytic for 2 weeks and only somnolence, lethargy without changes in blood tests and clinical examination were observed, with mild recovery. At the same time with trazodone were also administered drugs including non-steroidal anti-inflammatory drugs and antimicrobials and no adverse reactions were observed. Nonsteroidal anti-inflammatory drugs (carpofen, meloxicam, firocoxib, tepoxalin) and antibiotics (cephalosporins, amoxicillin with clavulanic acid, metronidazole, clindamycin, marbofloxacin) were administered for 7 days [2].

Table 1 (Adverse reactions in dogs studied and given trazodone approximately 3.5 mg/kg PO, q 12 hours) for calming and tramadol (4 to 6 mg/kg, PO, q 8 to 12 hours) for pain management after orthopedic procedures. The dose of trazodone was increased (approximately 7.0 mg/kg, PO, q 12 h) when tramadol was discontinued) [2].

Table 1. Adverse reactions in dogs studied and given trazodone as mentioned above

Side effects	Dogs not affected(%)
Diarrhea, loose stools	1(2.8)
Constipation	1(2.8)
Polydipsia	1(2.8)
Anxiety, restlessness	2(5.6)
Aggressiveness	1(2.8)
Drowsiness	5(13.9)
Groans	1(2.8)
Wheezing	2(5.6)
Incontinence	1(2.8)
Teething	1(2.8)
Hypersalivation	1(2.8)

The study was done on 17 dogs, 10 females and 7 males, all neutered, and trazodone was administered at a dose of 6.2 mg/kg. At the recommended doses, this anxiolytic does not alter the QT interval of the electrocardiogram, sinus rhythm occurring quite frequently, but also atrioventricular block of grade 1 and 2.

In healthy dogs, trazodone will decrease platelet aggregation by platelets, without affecting markers of hemostasis. After trauma and bleeding following surgery, hemostasis will be impaired, and trazodone is an important factor that aggravates bleeding and contributes to impaired primary hemostasis [14].

2. Methods used in trazodone studies

a. Preclinical studies (in vitro and in vivo)

In preclinical studies, the effects of trazodone on the central nervous system and other physiological functions shall be investigated. These studies help to understand the mechanism of action and to assess the toxicity and safety of the drug.

In vitro: Cell cultures are used to study the effect of trazodone on serotonergic receptors and other molecular targets. For example, neuron cultures may be used to observe how trazodone influences serotonergic transmission.

In vivo: Animal models (usually mice or rats) are used to assess behaviors associated with depression, anxiety and other conditions for which trazodone is

used. Behavioral tests include the learning task, assessment of motor activity, and assessment of physiological stress responses.

b. Clinical Trials

In clinical trials, the standard method is to compare the effects of trazodone with a placebo or with other drugs used to treat the same condition (e.g., antidepressants in the SSRI class). Clinical trials are usually organized in phases:

Phase I: Safety evaluation of trazodone in a small group of healthy volunteers to determine the maximum tolerated dose, side effects and pharmacokinetics of the drug.

Phase II: Conduct studies in small groups of patients suffering from conditions for which trazodone is prescribed to assess efficacy and safety.

Phase III: Testing trazodone in larger numbers of patients to confirm effectiveness and to observe long-term adverse effects.

3. Results and Discussions

3.1. Use of trazodone in geriatric patients

In order to use trazodone in this advanced age of patients, it is necessary to do a routine control because physiologically the organs reduce their functions and in case of using this anxiolytic some adverse reactions may occur. This routine check-up includes: taking the rectal temperature to check if it is normothermic, hypothermic or hyperthermic; palpation of the explorable lymph nodes: popliteal most frequently and submandibular to check if they are reactive; buccal and conjunctival mucosa if they are cyanotic, pale and jaundiced; respiratory rate to check if it is dyspneic; and heart rate. To find out if the heart is functioning normally, the stethoscope listens to the heart rate and can hear if there is any tachycardia, heart murmur or arrhythmias. Physiologically, in dogs the heart is arrhythmic but pathologically it will rhythmize. The rhythmic heart may in some cases also correlate with hyperthermia and is probably an infectious process. This listening may also correlate with an EKG to rule out possible heart failure, tachycardia, arrhythmia, atrioventricular block.

As investigations we can do: blood tests including: hemoleukogram and serum biochemistry because anxiolytics and anticonvulsants are metabolized in the liver and excreted by the kidneys. The first set of tests reveals whether there is already an infectious process in the body (neutrophils, lymphocytes and monocytes elevated) or not, an inflammatory process (C-reactive protein elevated in acute generalized inflammation, monocytosis, lymphocytosis elevated in chronic inflammation) or not, whether the patient is anemic (erythrocytes, hemoglobin and hematocrit), if dehydrated (increased red line), if the body's defense capacity is

impaired which may indicate decreased immunity of the body which may be caused either by stressors, various pathological factors (the main one being liver dysfunction in which coagulation factors are affected). The main indicator is PLT platelets/platelets/platelets.

The second set of analyzes is represented by biochemistry in which the liver parameters (AST, ALT, ALP, GGT, TBIL), kidney parameters (BUN, Urea, Creatinine), pancreatic parameters (AMY and Glucose) are within normal limits. Glucose increased a little over the lower limit may be due to stress caused by visits to the veterinarian, but much increased over the limits may be a possible diabetes mellitus [13].

Pancreatic amylase (AMY) being elevated we suspect possible pancreatitis and to be more certain canine and feline specific pancreatic lipase is also done. Aspartate and alanine aminotransferase are indicators for liver failure, and gamma-glutamyl transferase (GGT) and total bilirubin (TBIL) indicate gallbladder and cholecystic pathology, and the liver does not conjugate total bilirubin properly. If all liver factors are elevated, especially alkaline phosphatase well above the limits, and clinically we observe a distended abdomen and ultrasonographically fine fluid laminae through the abdomen, the prognosis is grave. In this clear case we suspect the presence of tumors or even liver cirrhosis. Increased calcium correlated with increased ALP indicates a malignant tumor. If phosphorus, urea and creatinine are elevated it leads to renal failure and according to this indicator it is divided into several grades. If this renal failure is not diagnosed in time and anxiolytics such as trazodone and anticonvulsants are administered, they are not eliminated from the body as well as the urine, causing the animal to autointotoxicate. If the renal indicators are at the upper limit, a more accurate indicator than creatinine is used, which correlates with the glomerular filtration rate, i.e. the GFR. This indicator increases in chronic kidney disease with loss of renal function by 30% to 40%, but creatinine will increase when more than 75% of renal function is impaired.

Further investigations include abdominal ultrasound where each organ is observed in more detail and X-rays to preventively rule out possible pulmonary metastases that may also spread to the brain. After the routine consultation and further investigations we can say whether in geriatric patients we can use trazodone or explain to the owners that we cannot risk aggravating their illness.

If these additional investigations are not done and trazodone is used in geriatric patients the risk of side effects is higher.

Trazodone is an antidepressant that takes effect after a single dose and is used alone in situations of situational anxiety (veterinary visits, car rides, fear of noise, separation disorder). It can also be used in combination with tricyclic antidepressants or selective serotonin reuptake inhibitors 2-3 times/day in general

anxiety and some forms of aggression. In combination with medications that increase serotonin concentrations lead to serotonergic syndrome (Citalopram, Escitalopram, Fluoxetine) (Table 2) [11].

Trazodone can be administered both per os and intravenously. The most tolerated route of administration is oral rather than parenteral. Among the more obvious side effects are tachycardia and uninhibited behavior. To minimize side effects if trazodone is given intravenously the dose will be substantially reduced. The per os route resulted in an acceptable absolute bioavailability (84.6%) [3].

Table 2. Doses of trazodone for behavioral and medical conditions [3]

Conditions	Dogs	Cats
Anxiety	1.9-16.5 mg/kg q24h for daily medication or 1.7-19.5 mg/kg q24h combined daily and as needed or 2.2-14 mg/kg q24h (as needed) for general anxiety 4-12 mg/kg q24h for 1.5 h before a veterinary visit	7.7-15.2 mg/kg q 24h for 1-1,5h before a visit to the doctor
Behavioral stress	3.7 mg/kg alone/combined with NSAIDs, tramadol or other drugs	No studies reported for the use of trazodone in cats
Sedation	3.5 mg/kg at 12-24h	10.6 to 33.3 mg/kg BW, PO, 1 to 1.5 hours before transportation/examination
Preoperative	5-7 mg/kg given 2 h before surgery combined with an opioid (Tramadol, Bupaq/Alvegesic) as premedication for anesthesia and orthopedic surgery	No studies are reported for this endpoint
Postoperative	1-3.5 mg kg in combination with tramadol for 3 days and then 7 mg kg-1q 12 h or 7-10 mg kg-1q 8 h as needed for 4-12 weeks for orthopaedic surgery	No studies are reported for the use of trazodone in cats

This anxiolytic has been administered to puppies mostly canned or rewards especially for those exhibiting some with sensitivities or dietary restrictions. They were constantly monitored whether they consumed the drug or not. The amount of trazodone administered will not exceed the dose of 300mg-600mg in 24 hours. Administration was started at 4 mg/kg at 12 h or in doses of 10-12 mg/kg at 8 h intervals for the desired calming and anxiolytic effects in some dogs undergoing surgery. Administration of trazodone continued throughout their hospitalization as needed, with adjustments made to account for changes in signs of anxiety [7].

Trazodone has a much higher risk of adverse reactions in geriatric patients including: callus, vomiting, colitis, sedation, sedation, increased appetite,

paradoxical excitement and panting, hypersalivation and disinhibited behavior in dogs, and in cats are those of hypersalivation, paradoxical excitement, ataxia, vomiting, diarrhea, callus (3).

3.2. Effects of trazodone on social behavior in dogs and cats

Stress caused by hospitalization in dogs and cats has negative effects on social behavior. Dogs that are hospitalized suffer from acute as well as chronic psychological stress due to separation from family members. The main methods of stress assessment are physiological measurements as well as behavioral observations [7].

Physiological variables include assessment of hormones on the hypothalamic-pituitary-adrenal axis (the main hormone of interest being cortisol), heart rate variability, salivary immunoglobulin A and the neutrophil-to-lymphocyte ratio (the white line being low in cases of stress). By observing behavioral signs we look for the following: anxiety, changes in locomotion and posture, vocalizations, phobias, phobias, increased excitement, fear, panting, attempts to run away, but especially facial expressions (intense lip licking). These changes in the social behavior of animals differ depending on the intensity and type of stimuli to which they have been subjected [7].

Psychogenic and physical stressors most commonly affect dogs that are housed in shelters due to reduced opportunities to move around, a new place compared to what they were used to, change in daily routine [1].

These disruptive factors have adverse effects on health status including: suppression of the immune system which implicitly leads to a higher percentage of infectious-contagious diseases, increased susceptibility and severity of infections, slowing of wound healing processes as well as immune responses to vaccines. The main mechanism is the impairment of the body's homeostasis due to increased plasma concentrations of corticosteroids (adrenocorticoids as well as cortisol). Plasma adrenocorticoid levels can increase within 4 hours in a new shelter. Cortisol concentrations during the first 3 days of a dog's stay in a kennel are three times higher than in a dog living in an apartment with its owners [1].

The most commonly used anxiolytic with low side effects, trazodone hydrochloride, is recommended to moderate stress. It is highly bioavailable and very well tolerated. The dose is 5 mg/kg and will be administered in 2 doses: the first dose before the dog's arrival in the kennel and the second dose on the morning of the following day. If the protocol will be followed, then the 48 h transition period - i.e. the transition from its natural environment to another environment, namely the kennel - will be properly managed. For each dog, data is collected on: when and for how long they have been in the shelter, whether or not they are up for adoption, whether or not they have been given

anxiolytics/tranquilizers other than trazodone, reunion with the owner, placement with other dogs in the kennel, whether or not they have infectious respiratory diseases, plus euthanasia for medical and behavioral reasons. It can be administered to any breed of dog, and sex and age are irrelevant [1].

If trazodone is administered within the first 48 hours to dogs in the kennel, the incidence of respiratory disease will be significantly reduced. This anxiolytic will not affect already sick dogs, but decreases the likelihood of them becoming ill. Those given Trittico unlike those not given anxiolytics will be adopted much more quickly and do not develop respiratory disease. These diseases are more common in dogs kept in paddocks [1].

In cats, the main behavioral problem is when owners want to put them in a transport cage to go for a routine medical checkup. In this situation, cats resist when they have to be caged but in these situations they can also become aggressive towards their owners. The stress caused by isolation and transportation can lead to states of excitement or anxiety which make it difficult to handle and examine them. In these cases, there is a high chance that both the veterinarian and the owner will be injured because the cats are trying to appear. These stressors can lead to decreased quality of patient care. If the cats are anxious so will be the owners who feel that the traumatizing event caused by the visit to the doctor affects the animal's health much more than the lack of care at the doctor [8].

In order to reduce the stress associated with visits to veterinary surgeries, owners must be highly trained to administer trazodone prior to transportation or hospitalization. This anxiolytic gives promising results in cats, and in dogs it is very effective being anxiolytic as well as sedative. Stress in cats was assessed at 3 time points: pre-examination, examination and post-examination by scores ranging from 1 (relaxed) to 7 (terrorized). Stress scores for the three time points were combined on an overall score. Behavioral respon.ses to the examination were also recorded and scored for six different behavioral manifestations (vocalization, fight, aggression, hypersalivation, immobility response, and mouth-breathing) and all these scores are combined on an overall score [16].

Trazodone in cats gives satisfactory results and very rare side effects including: anorexia, vomiting, diarrhea, ataxia, tremor, paradoxical excitation or behavioral disinhibition in any cat during the study. This anxiolytic is of different concentrations: 50 mg,75 mg and 100 mg. The best effect was produced after administration of trazodone at a concentration of 100mg/33.3 mg/kg in food and occurred within 2 to 2.5 hours. In adult cats, a dose of 50 mg/piquid or 10.6 mg/kg is also recommended. If to be given daily the dose is 1-2 mg/kg every 12hrs. Not to be used in combination with macrolides, phenothiazides or azole antifugals. Avoid administration in renal, hepatic, cardiac and glaucoma [19].

In addition to the administration of trazodone, a positive role on the reduction of acute or chronic stress, behavior but also on the healing of possible injuries is the social interactions. Having a dog or cat with a companion significantly reduces cortisol concentrations secreted by the adrenal cortex and increases the production of proinflammatory cytokines that stimulate wound healing. In contrast, psychological stress inhibits these mechanisms and in particular suppresses the production of interleukin (IL)-1b and interleukin IL-8 which are the main mediators of wound healing. Social interactions not only significantly reduce the risk of disease but also contribute to the body's increased immunity [4].

If stress injuries are not healed in time, the animal's health can be worsened because there is a high risk of opportunistic infections, especially in dogs and cats that are socially isolated or have comorbidities/diseases that affect the body's defense capacity (diabetes mellitus, diabetes insipidus, malignant tumors, FIV/FeLV in cats, autoimmune diseases e.g. systemic lupus erythematosus). Stress frequently predisposes animals to bacterial infections [18].

Fear, stress and anxiety severely affect the health status of animals, but especially their owners, and make it difficult for veterinarians to work and handle them. By implementing a "Fear Free" approach will significantly improve the health, well-being and safety of pets, their owners and veterinarians. If states of stress and anxiety persist for a long time and are not properly managed, then changes in the pet's general condition and physiological constants (significant increases in heart rate, blood pressure, respiratory rate and rectal temperature occur) [18].

The body's stress response serves as a coping mechanism. In the acute, the sympatho-medullary system will be activated, releasing adrenaline and nor-adrenaline, but also the hypothalamic-pituitary-adrenal axis, which will produce cortisol and vasopressin over the limits and will increase glucose, heart rate and urine output. Initially, under the influence of stressors, defense mechanisms will be stimulated to boost immunity. If the stressors are intentional and persist for a long time or it is after an immune disturbance, the immune response is suppressed, wounds will heal much later and susceptibility to infection will increase. Another important change is the increase in the urea-creatinine ratio in urine especially when hospitalized for monitoring. Urea-creatinine concentrations will persist even 12 h after discharge. A differential diagnosis should be made from hyperadrenocorticism especially from diabetes mellitus [17].

Blood tests will be performed, first of all serum biochemistry and we observe if glucose values show specific elevations -possible diabetes- but also non-specific elevations in case of stress. Normal blood glucose values in dogs are 67-125 mg/dl and in cats 70-160 mg/dl. If the values are slightly elevated 140-180 mg/dl the treatment will be limited to a diabetic diet, if the values are between 180-240

mg/dl, the diet will be supplemented with oral hypoglycemic agents: Meguan, Maninil, Novonorm, Fitodiab, blueberry capsules. In the latter situation, if the values are elevated above 250 mg/dl and the glucose over 500 mg/dl, insulin treatment is started. Most commonly, Mixtard mixed-acting, rapid 30% and delayed 70% twice daily will be used. The insulin dose in dogs is 0.5-1 IU/kg/day and in cats 0.25-0.5 IU/kg/day [17].

If the stress is of chronic nature, then mental disorders, disorders of the digestive (gastrointestinal), respiratory, cardiovascular, renal, reproductive systems occur and frequently predisposes especially to dermatitis. In cases of anxiety and depression in the forelimbs, psychogenic alopecia occurs due to persistent licking. Cats in colonies are the most affected due to chronic stress and it is manifested by gastrointestinal disturbances but also most often they will not groom themselves [17].

In pathological behavioral disorders anxiolytics and anticepressants are used:

a) Serotonin 2A receptor antagonist and has a secondary mechanism of reuptake inhibition of the brain neurotransmitter reuptake inhibitor being classified as SARI: Trazodone;

b) Benzodiazepines: alprazolam, chlorazepate, diazepam, midazolam, oxazepam, clonazepam, lorazepam and temazepam;

c) Tricyclic antidepressants: TCA; amitriptyline, nortriptyline, clomipramine, imipramine and doxepin);

d) Selective serotonin reuptake inhibitors: SSRIs; fluoxetine, paroxetine, sertaline, fluvoxamine, venlafaxine,citalopram and escitalopram);

e) Noradrenergic and specific serotonergic antidepressants: mirtazapine;

f) Centrally acting alpha-adrenergic receptor agonists: clonidine, guanfacine, medetomidine and dexmedetomidine; dexmedetomidine also affects alpha1A receptors [17].

The most commonly used anxiolytic in veterinary practice is trazodone which gives satisfactory results in behavioral disorders in dogs and cats. The most frequent in dogs are: separation anxiety, generalized anxiety disorder, noise phobias, aggression and deep-seated fears and in cats: deep-seated fears, aggression and anxiety affecting different types of inappropriate urination [15].

For example, in cats is present that stressor factor that consists in the fact that they are born in extended matrilineal family groups that within households these families will mix and a behavioral pathology. Normally, cats are very active because they are in search of food [15].

Normal behavior in dogs is that of friendship and socialization with humans. For example, some dogs are used for hunting, drug-sniffing, or when a danger is around they or their owners will do their best to get rid of it, and if they don't realize the threat is coming, they will persist until they do. Dogs and cats suffer most when their owners leave home for a long or short period of time or are died [15].

Among the most common behavioral disorders are obsessive-compulsive disorder, separation anxiety, phobic reactions to noise, fear of new places and experiences, and generalized anxiety [15].

Trazodone mostly in dogs and cats presents a variable dose between 1.7-9.5 mg/kg/day and most commonly in addition to relieving depression and anxiety will be used in order to reduce the panic brought on when cats are brought to the veterinarian. It is also useful in panic disorders and phobias as an adjunct to treatment with benzodiazepines, TCA- tricyclic antidepressants and SSRI-selective serotonin reuptake inhibitors. Because veterinarians have perceived trazodone to be "mild" and "safe," it is now routinely administered for many forms of distress (both inpatient and outpatient). The potential risks of serotonergic serotonergic syndrome are usually not much discussed [15].

3.3. Effects of trazodone on post-surgical interventions in dogs and cats

Stress in dogs and cats is frequently caused by the visit to the veterinarian's office having a negative impact on the animals, the owners and especially the veterinarians who will make their work more difficult. In addition to this stress factor, others are the possible surgery and hospitalization for 5-6 days for post-operative supervision. In this case, the recovery period will be prolonged for a long time negatively affecting animal welfare [3].

To reduce the stress of the animal and the doctor, to facilitate calming and isolation of the dogs/pisies from the owner it is recommended to administer trazodone, the main anxiolytic which is a serotonin antagonist/reuptake inhibitor having a complex activity on serotonergic systems. This anxiolytic has minimal effects on muscarinic cholinergic receptors with few anticholinergic side effects [8].

Serotonin is a neurotransmitter released by serotonergic neurons found in many parts of the brain. It originates in the brainstem and influences the rostral system, which regulates body temperature, wakefulness, food intake and emotional behavior. Serotonergic serotonergic syndrome occurs due to excess serotonin in synapses in different areas of the brain and the main mechanisms are: increased serotonin synthesis/release, direct stimulation of receptors or an inhibition of serotonin reuptake. The manifestations of serotonergic syndrome are represented by the triad:

a) nervous disorders among the most common (hyperarousal, confusion, delirium, ataxia, tremor);

b) hyperactivity of the autonomic nervous system (hyperthermia, hyperhidrosis, tachycardia, tachypnea);

c) neuromuscular abnormalities (muscle rigidity, shivering) [13].

At first, the clinical signs of this triad are of low intensity and then gradually intensify with muscle hypertonemia, hyperthermia, and serious life-threatening signs [5].

This serotonergic serotonergic syndrome is most often caused by the combination of the main opioid tramadol and selective serotonin reuptake inhibitors SSRIs at the same time with the aim of reducing the stress caused by post-surgical interventions. Avoiding the use of SSRIs is not really possible because other antidepressants, including tricyclic antidepressants and serotonin and norepinephrine reuptake inhibitors (SSRIs), such as venlafaxine, also increase serotonin concentrations at postsynaptic receptors. These SSRI antidepressants exert their effects by binding to serotonin reuptake transporters in the synaptic cleft of the central nervous system, thus preventing serotonin reuptake. This will result in an increase of the neurotransmitter in the synaptic cleft and they are therefore CYP2D6 inhibitors. Tramadol is a central nervous system analgesic opioid that undergoes extensive metabolism, resulting in 23 metabolites, including the metabolite O-desmethyltramadol (M1) created by CYP2D6 enzymes. This M1 metabolite has a 200-fold increased affinity for the μ-opioid receptor contributing to the analgesic effect. If trazodone is not available, non-steroidal anti-inflammatory drugs or even paracetamol can be used [5].

Attention should be paid to trazodone and other antidepressants because they are associated with an increased risk of prolongation of the electrocardiogram (EKG) QT interval and arrhythmias. Another quite important adverse reaction is primary hemostasis. Prior to administration, a comprehensive clinical examination should be done and it should be seen what medications have been administered before, previous illnesses manifested by altered heart rhythm, QT prolongation, impaired primary or secondary hemostasis. Other examinations are blood smear evaluation for platelet aggregates, chemical profile, urinalysis, prothrombin time (PT), partial prothrombin time (PTT) and an electrocardiogram. Dogs with pathology, those on medication except those receiving preventive deworming were excluded from the study [2].

3.4. Dental use of Trazodone

Before the animal comes in for dental evaluation with a possible extraction or scaling, the cat or dog will undergo a general consultation followed by blood tests (hemoleukogram and serum biochemistry). If all goes normally, anesthetic procedures will be performed in the morning and early afternoon to give patients sufficient time to recover under the close supervision of our nursing staff before

discharge. Otherwise, when details such as unexplained recent unexplained weight loss, a new heart murmur, or other indications of a potential medical problem are present at anesthesia, they will be immediately investigated [13].

The night before the dental procedure, the animal is not allowed to drink water or eat after 22:00. In certain situations when the animal is very stressed, aggressive and anxious, anxiolytics may be prescribed, the most commonly used of which are gabapentin and trazodone to reduce the intensity of these states of nervous excitation. These pills can be administered in food per os and are available as trazodone hydrochloride oral tablets 50, 100, 150 and 300 mg [13].

The order in which your pet will be anesthetized will depend on: a variety of factors, including your pet's level of dental disease, level of anxiety and pre-existing medical conditions [13].

To undergo anesthesia safely, the pet will be sedated with a mild sedative for pain relief by intramuscular injection: Domitor. After the mild sedative, an intravenous catheter will be placed. Through this catheter induction drugs are administered: intravenous anesthetics. The induction drugs take effect quickly and the pet does not feel anything during the medical procedure. He will be intubated by placing an anesthetic tube in the trachea through which inhalation gases will be administered to maintain anesthesia and oxygen throughout the dental procedure [13].

The use of an intravenous catheter and tracheal intubation enhances the safety of anesthesia by allowing the medical professional direct access to the airway and circulatory system. The dental procedure lasts approximately 1-3 h, and this duration of anesthesia can be safely maintained only in the manner described. The vital parameters of the pet, including temperature, heart rate with EKG, respiratory rate are closely and constantly monitored by the medical staff [14]

Trazodone should be used with caution especially in geriatric patients, especially those with liver, kidney and heart disease. It is an antidepressant that inhibits the serotonin transporter and serotonin type 2 receptors; it is a triazolopyridine derivative. Trazodone inhibits serotonin reuptake and blocks histamine and α-1-adrenergic receptors. The drug also induces significant changes in presynaptic 5-HT adrenoreceptor receptors. It belongs to the category of SARI drugs (serotonin antagonists and reuptake inhibitors), other drugs being: phenylpiperazine, etoperidone, lorpiprazole and mepiprazole. It is comparable in efficacy to other classes of drugs such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine receptor blockers [14].

The main side effects of trazodone include headache, dizziness, drowsiness. Other risks include anticholinergic effects such as: dry mouth, hypotension, syncope, syncope, QT prolongation and priapism. The QT prolongation and arrhythmia risks are due to trazodone's interaction with potassium channels.

Despite the presence of anticholinergic effects, the risk of urinary retention and constipation is lower than tricyclic antidepressants such as imipramine or amitriptyline. The risk of hypotension is higher in geriatric patients, especially those with pre-existing heart disease, due to blockade of α1 adrenergic receptors. Patients usually experience side effects of somnolence and hypotension during the first week of administration. In some cases, trazodone use has been correlated with visual hallucinations. Hallucinations generally resolve with discontinuation of trazodone, and clinicians should switch the patient to another antidepressant medication [13].

The degree of morbidity, the age of the animal, the number of animals treated and the number of drugs prescribed are factors that may influence the incidence of drug interactions. Certain physiological changes occur in geriatric animals, which merit attention when administering drugs. With increasing age, there is a decrease in the function of the liver and kidneys, which are responsible for the metabolism and excretion of administered drugs [10]. Lack of interest in maintaining oral hygiene in depressed patients is often accompanied by a high-carbohydrate diet and reduced salivation. Several commercially available antidepressants cause the side-effect of xerostomia, which results in a change in the oral flora, reduced tissue self-cleansing, a loss of buffering capacity, an increased risk of plaque accumulation, gingivitis, periodontitis, caries, candidiasis and sialadenitis [13]. Hyposalivation reduces mucosal lubrication, which in turn has an adverse effect on the risk of oral mucosal injury and retention of removable dentures. Therefore, animals with nervous inhibition often require dental treatment as a consequence of their underlying disease or the pharmacotherapeutic agents they are taking [10].

Common adverse interactions between antidepressant drugs and drugs commonly administered in dentistry:

A) Interactions with vasoconstrictors

The administration of vasoconstrictors as an additive to local anesthetics: (adrenaline, noradrenaline, α-methyl noradrenaline, isoprenaline and phenylephrine) during antidepressant treatment with tricyclic antidepressants (TCA) (Table 1), bupropion, maprotiline (Table 2) or St. John's wort (Table 3) may lead to adverse interactions, which manifest as an increase in the effect of vasoconstrictors on the circulatory system [10]

Table 3. Possible interactions with vasoconstrictors and TCAs

Antidepressant TCA	Antidepressant interaction with vasoconstrictors
	transient potentiated sympathomimetic activity
	increased systolic blood pressure with significant increase in central arterial and venous pressures
	severe hypertensive reaction
	severe respiratory depression, cardiotoxicity, death

Antidepressants relevant to oral and maxillofacial surgical practice - PMC (nih.gov)

Table 4. Possible interactions with vasoconstrictors and maprotiline, bupropion

Maprotiline	increased mean arterial pressure and central venous pressure due to adrenaline and especially alpha-methylnoradrenaline
Bupropion	Hypertensive reaction

Antidepressants relevant to oral and maxillofacial surgical practice - PMC (nih.gov)

The increase in pressure during administration of a TCA is due to inhibition of neuronal reuptake of the vasoconstrictor (Table 4). Intravenous administration of adrenaline or noradrenaline in healthy subjects resulted in a two- to eight-fold increase in the pressure response to the vasoconstrictor (Table 5) [13].

Table 5. Possible interactions with NSAIDs and antidepressants

Antidepressants	Interaction with :	Mechanism	Consequences
SSRIs	Aspirin	Reduction of serotonin receptors on the platelet surface, reduction of platelet binding affinity and platelet secretion in response to collagen, block calcium mobilization in platelets.	Increased risk of gastrointestinal bleeding
	NSAIDs	Reduction of serotonin receptors on the surface of platelets, block reuptake of serotonin into platelets, reduce platelet aggregation and platelet activity.	Increases the risk of 3- to 12 h risk of gastrointestinal bleeding.

Antidepressants relevant to oral and maxillofacial surgical practice - PMC (nih.gov)

Table 6. Interactions with benzodiazepines

Antidepressant	Interaction	Other interactions	Mechanism
Lithium	Increased sedation	Hypothermia	
Valproate		Psychotic episodes	
Nefazodone		Increased serum level and prolonged half-life of benzodiazepines, psychomotor impairment	Influence on the appropriate degradation by inhibition of CYP 3A
SSRIs			Influence on appropriate degradati by inhibition of the metabolizing C isoenzymes (CYP 3A4, CYP 2C9, CYP 2C19, CYP 2D6)
TCAs		Increased toxicity of antidepressants, undesirable respiratory depression, orthostatic hypotension	
MAOIs		Intensified effect and increased toxicity of antidepressants, hypertensive crises	

Antidepressants relevant to oral and maxillofacial surgical practice - PMC (nih.gov)

Drug interactions should be anticipated when benzodiazepines are administered during treatment with most common antidepressants (Table 6). Hepatic metabolism of benzodiazepines may be increased by CYP 3A4 isoenzyme inducers [13].

The macrolide antibiotics erythromycin and clarithromycin, by inhibiting CYP 3A4 and CYP 1A2 isoenzymes, influence the hepatic metabolism of a large number of drugs, which may enhance their effects (Table 7) [10].

Table 7. Interactions with antibiotics: macrolides and fluoroquinolones

Macrolide	Antidepressants	Mechanism	Consequ
Erythromycin	Heterocyclic derivatives	Reduction of antibiotic effect via induction of the metabolizing CYP 3A4	
	St. John's wort		
	Lithium	Increased serum level of lithium	Increased
	Valproate	Increased serum levels of	side effec
Erythromycin/ clarithromycin	Carbamazepine	antidepressants because of inhibition	toxicity of
	TCAs	of hepatic metabolism	
	SSRIs		

TCAs = Tricyclic antidepressants, SSRIs = Selective serotonin reuptake inhibitors

Antidepressants relevant to oral and maxillofacial surgical practice - PMC (nih.gov)

Conclusions

(1) Trazodone is the main anxiolytic used in veterinary medicine to reduce physiologic stress in cats and dogs when they are brought to the veterinarian.

(2) Stress in dogs and cats is frequently caused by a visit to the veterinarian's office and has a negative impact on the animals, the owners and especially the veterinarians who will make their work more difficult. In addition to this stress factor, others are the possible surgery and hospitalization for 5-6 days for post-operative supervision. In this case, the recovery period will be prolonged for a long time negatively affecting the welfare of the animals. Tra trazodone which is a serotonin antagonist with few anticholinergic side-effects should be used as the main anxiolytic.

(3) In addition to trazodone, which is the most effective anxiolytic, other drugs can also be used, including gabapentin, alprazolam and dexmedetomidine taken orally. The former is also used successfully in post-surgical interventions.

(4). It is commonly used because it rarely presents side-effects including: headache, vomiting, ataxia, ataxia, asthias, priapism. If used concomitantly with selective serotonin reuptake inhibitors (SSRIs) including: Citalopram, Escitalopram, Fluoxetine, etc. or with tricyclic antidepressants (TCA): Imipramine, Amitriptyline, Doxepin should be supervised frequently as there is a major risk of serotonin syndrome. The main symptoms are: hyperthermia, diarrhea, tremors, hypertension being common in cats, tachycardia, behavioral changes but especially seizures.

(5). In order to use trazodone in geriatric patients, a routine control should be made because physiologically the organs reduce their functions and in case of using this anxiolytic some adverse reactions may occur. This routine control includes: control of rectal temperature; palpation of explorable lymph nodes: popliteal and submandibular; oral and conjunctival mucosa; respiratory rate; heart rate and blood tests: hemoleukogram and serum biochemistry.

(6). Doses of trazodone differ according to conditions: in anxiety the dose in dogs is :1.9-16.5 mg/kg q24h for daily medication or 1.7-19.5 mg/kg q24h combined daily and as needed administration or 2.2-14 mg/kg q24h (as needed administration) for general anxiety 4-12 mg/kg q24h for 1.5 h before a veterinary visit. In cats the dose is 7.7-15.2 mg/kg q 24h for 1-1.5h before a veterinary visit. In behavioral stress the dose in dogs is: 3.7 mg/kg alone/combined with NSAID, tramadol or other drugs and in cats no studies are reported. Preoperatively and postoperatively in cats there are no dose studies recorded and in dogs the doses are 5-7 mg/kg given 2 h before surgery combined with an opioid (Tramadol, Bupaq/Alvegesic), respectively 1-3.5 mg kg combined with tramadol for 3 days and then 7 mg kg-1q 12 h or 7-10 mg kg-1q 8 h as needed for 4-12 weeks for orthopedic surgery.

(7). Disruptive factors have adverse effects on health including: suppression of the immune system which implicitly leads to a higher percentage of infectious diseases,

increased susceptibility and severity of infections, slowing of wound healing processes as well as immune responses to vaccines.

(8) The most commonly used anxiolytic in veterinary practice is trazodone which gives satisfactory results in behavioral disorders in dogs and cats. The most common in dogs are: separation anxiety, generalized anxiety disorder, noise phobias, aggression and deep-seated fears and in cats: deep-seated fears, aggression and anxiety affecting different types of inappropriate urination. In this case the doses in cats are 50 mg,75 mg,100 mg in cats the latter being very effective. In dogs the dose is 5 mg/kg and is administered in 2 doses: the first dose before the dog's arrival in the kennel and the second dose on the morning of the following day.

(9)Trazodone mostly in dogs and cats presents a variable dose between 1.7-9.5 mg/kg/day and most commonly in addition to relieving depression and anxiety will be used in order to reduce the panic brought on when cats are brought to the veterinarian.

R E F E R E N C E S.

[1] Abrams, J., Brennen, R., Byosiere, S.-E., Trazodone as a mediator of transitional stress in a shelter: Effects on illness, length of stay, and outcome, Journal of Veterinary Behavior, 36 (2020) 13-18 (2020).

[2] Benjamin, E.J., Nelson, O.L., Baumwart, R., Haines, J. Adverse effects of trazodone in dogs on primary hemostasis and electrocardiogram: A single-blinded placebo-controlled crossover study. J Vet Intern Med. 37(6): 2131-2136.doi:10.1111/jvim.16841. (2023)

[3] Chea, B., Giorgi, M., Trazodone: A Review of Its Pharmacological Properties and Its Off-Label Use in Dogs and Cats, American Journal of Animal and Veterinary Sciences 12 (4): 188.194 DOI: 10.3844/ajavsp.pag.188-194 (2017).

[4] Detillion, E.C., Craft, K.S.T., Glasper, R.E., Prendergast, J.B., DeVries, A.C., Social facilitation of wound healing, Elsevier, pp. 1004-1007 (2003).

[5] Dillon, L. The efficacy of trazodone in reducing stress related behaviours in hospitalised dogs or dogs confined postsurgery. Veterinary Evidence, 8(2), 1-9. https://doi.org/10.18849/ve.v8i2.550, (2023).

[6] Erickson, A., Harbin, K., MacPherson, J., Rundle, K., Overall, L.K., A review of pre-appointment medications to reduce fear and anxiety in dogs and cats at veterinary visits, Can Vet J, Vol.62, pp..955-957 (2021).

[7] Gilbert-Gregory, E.S., Stull, W.S., Rice, M.R., Herron, E.M., Effects of trazodone on behavioral signs of stress in hospitalized dogs, JAVMA, 249(11), Pp.1283, pp.1288-1289 (2016).

[8] Gruen, M.E., Sherman, B.L. Use of trazodone as an adjunctive agent in the treatment of canine anxiety disorders: 56 Cases (1995–2007). J Am Vet Med Assoc. 233(12):1903–1905. [PubMed: 19072606] (2008).

[9] Gruen, M. E., Roe, S. C., Griffith, E., Hamilton, A., & Sherman, B. L. (2014). Use of trazodone to facilitate postsurgical confinement in dogs. Journal of the American Veterinary Medical Association, 245(3), 296-301. Retrieved Jun 30, 2024, from https://doi.org/10.2460/javma.245.3.296

[10] Lambrecht, J.T., Greuter, C., Surber, C. Antidepressants relevant to oral and maxillofacial surgical practice. Ann Maxillofac Surg. 3(2):160-6. doi: 10.4103/2231-0746.119233. PMID: 24205476; PMCID: PMC3814665. (2013 Jul.)

[11] Landsberg, G., Sekse, K., Making sense of behavioral medications: a practical approach to their use in dogs and cats, NAVC Conference, pp.119-121 (2017).

[12] Lueck, L.C., Cameron, S., Zidan, N. Effects of trazodone administration on the neurologic examination in healthy dogs. J Vet Intern Med. 36(6): 2142-2148. doi:10.1111/jvim.16536; (2022).

[13] Manani, G., Paniz, P., Beltrame, A., Brunelli, G.F., Zanardi, L., Piranese, A. Analisi in doppio cieco delle possibilità di impiego del trazodone nella sedazione del paziente odontoiatrico ambulatoriale [Double-blind analysis of the possibilities of the use of trazodone in sedation of ambulatory dental patients]. Minerva Stomatol. 28(3):193-200. Italian. PMID: 399320; (1979 Jul-Sept.).

[14] Medline Plus. Trazodone: Medline Plus Drug Information, https://medlineplus.gov/druginfo/meds/a681038.html#:~:text=Trazodone%20is%20used%20to%20treat,that%20helps%20maintain%20mental%20balance. Accessed on Sept. 2, 2024

[15] Nelson, M.E., Philbrick, M.A., Avoiding Serotonin Syndrome: The Nature of the Interaction Between Tramadol and Selective Serotonin Reuptake Inhibitors, The Annals of Pharmacotherapy, Vol.46, pp.1712-1714 (2012).

[16] Orlando, M.J., Case, C.B., Thomson, E.A., Griffith, E., Sherman, L.B., Use of oral trazodone for sedation in cats: a pilot study, Journal of Feline Medicine and Surgery, 18(6) 476–482 (2016).

[17] Overall, L.K., Behavioral Pharmacotherapeutics, Pharmacotherapeutics for Veterinary Dispensing, First Edition, pp..378-390 (2019).

[18] Radosta, L. Behavior is Medicine. Fear Free is Better Medicine, Fear Free Symposium Lisa Radosta Proceedings, pp.2-6 (2018).

[19] Stelow, E. Feline Psychopharmacology, Clin News on the use of trazodone in veterinary medicine News on the use of trazodone in veterinary medicine News on the use of trazodone in veterinary medicine ical Handbook of Feline Behavior Medicine, First Edition, p. 281(2023).