

PRACTICAL PHARMACOLOGY

What's New With Feline-Friendly Previsit Pharmaceuticals

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In the United States, approximately 61 million cats are kept as companions; however, less than half of owned cats visit the veterinarian annually, and cats are more likely than dogs to never visit a veterinarian or only visit the veterinarian on an emergency basis.^{1,2} One barrier to veterinary care of cats is the fear, anxiety, and stress associated with transportation and veterinary visits.³ Another factor is the perception that cats are self-sufficient. To the contrary, cats are adept at disguising illness for the purpose of survival.

Common medical issues of cats that could be diagnosed with routine veterinary care include obesity, kidney disease, endocrine disease, osteoarthritis, and dental pain. To further challenge veterinarians, many physical

examination parameters of cats are difficult to obtain or are altered by stress or required sedation (e.g., cardiac auscultation [tachycardia, stress-induced murmurs], accurate blood pressure measurement, meaningful orthopedic and neurologic examinations).³ Complete therapy for feline fear, anxiety, and stress includes behavioral modification (desensitization and counterconditioning) and pharmacologic treatment.

Current medications used off label for treatment of acute feline anxiety and fear associated with transportation and veterinary visits include gabapentinoids (e.g., gabapentin, pregabalin), benzodiazepines (e.g., alprazolam, lorazepam), and trazodone (**TABLE 1**). Use of acepromazine as a sole

Abstract

To facilitate appropriate veterinary care for feline patients while protecting their mental health, practitioners have moved to premedicating cats with anxiolytics before transportation and examination. Premedication has most commonly involved off-label use of gabapentinoids and trazodone. However, a U.S. Food and Drug Administration-approved formulation of pregabalin flavored oral solution was recently released. Clinical studies showed the Schedule V controlled substance to be efficacious for reducing acute feline fear during transportation and veterinary visits. Healthy cats exhibited minimal sedation and side effects. Compared with gabapentin, pregabalin is more potent, requires a smaller dose, and has a longer duration of action.



Take-Home Points

- An oral solution of pregabalin was recently approved for treatment of feline acute fear, anxiety, and stress associated with transportation and veterinary visits.
- For cats that associate veterinary visits with fear, anxiety, and stress, multimodal treatment (e.g., previsit pharmaceuticals, appropriate handling, desensitization and counterconditioning) is essential.
- Pregabalin decreases the release of excitatory neurotransmitters in the central nervous system, dampening the stress response with minimal sedation.
- Clinical studies have demonstrated pregabalin's safety at 5 mg/kg; lower doses are recommended for cats with renal dysfunction.
- At higher doses, pregabalin may cause cardiovascular effects, including hypotension or bradycardia resulting in reflex hypertension.
- Use of pregabalin may potentially be useful for treatment of feline neuropathic pain.

agent has fallen out of favor for previsit use due to its pure sedative effect and lack of anxiolytic effects. Benzodiazepines are not generally favored due to their potential for paradoxical excitement and disinhibition of aggression.⁴

TRAZODONE

Several studies have documented the role of trazodone in reducing feline previsit and examination anxiety, although it has a bitter flavor and may cause gastrointestinal upset. A pilot study showed sedation but no change in behavior during examination in laboratory cats given 100 mg of trazodone orally.⁵ A study of healthy owned cats demonstrated that those receiving 50 mg of oral trazodone showed significant improvement of client-assessed transportation and veterinarian-assessed examination anxiety, and the dose was well tolerated by most cats.⁶ Transdermal trazodone at 150 mg/cat decreased previsit and postvisit (transportation) as well as examination anxiety scores and did not affect vital parameters including blood pressure.⁷

GABAPENTIN

Use of gabapentin to reduce previsit anxiety in cats has become more popular in the past decade. A randomized, blinded, crossover clinical trial of 20 cats demonstrated that a single dose of 100 mg/cat given 90 minutes before transportation was safe and significantly reduced client perception of transportation stress and veterinarian perception of handling compliance.⁸ Studies of gabapentin in community cage-trap-confined cats given 50 to 100 mg resulted in reduced fear responses.⁹ A crossover study assessed the

blood pressure of 6 cats in various settings, each of which had a surgically implanted femoral artery telemetric blood pressure-sensing catheter, and found no difference between cats orally administered 100 mg of gabapentin or placebo.¹⁰ A randomized, blinded, placebo-controlled crossover study of 29 cats that measured systolic blood pressure via Doppler ultrasonography and sphygmomanometry 3 hours after oral administration of 10 mg/kg gabapentin revealed a significant decrease (median 12 mm Hg) in the blood pressure of treated cats.¹¹

BOX 1 Pregabalin Compared With Gabapentin*

Pregabalin

- Available as a U.S. Food and Drug Administration-approved suspension
- Causes less sedation
- Is more potent
- Has a longer duration of action
- Is easier to dose (smaller volume of flavored liquid)
- May affect blood pressure (high or low) at higher doses
- Is controlled (Schedule V drug)
- Is more expensive

**The efficacy of pregabalin and gabapentin for prevention of feline acute fear and anxiety has not been compared in a head-to-head study. However, evaluation of independent studies indicates the above for pregabalin.*

Gabapentin has been found to be ineffective when administered transdermally.¹² A recent study that evaluated serum concentrations of gabapentin in cats with stable International Renal Interest Society stage 2 chronic kidney disease found that cats that received 10 mg/kg orally had significantly higher dose-normalized serum gabapentin concentrations than healthy cats that received a single 20 mg/kg dose orally.¹³ The study authors recommended reducing the dose of gabapentin for cats with chronic kidney disease.

PREGABALIN

Pregabalin oral solution for cats (Bonqat; Zoetis, zoetisus.com) is the first on-label option for treatment of acute fear and anxiety associated with transportation and veterinary visit stress available in both the United States and Europe.¹⁴ Pregabalin is similar to gabapentin in terms of mechanism of action, safety, and efficacy, with some notable differences (**BOX 1**).

Dosing and Administration

Bonqat is supplied as a 50 mg/mL pregabalin solution, to be stored at 2 °C to 8 °C (36 °F to 46 °F) for up to 6 months after the 2-mL bottle is opened. Bonqat is a Schedule V controlled substance with abuse potential and must be stored and documented as required by law. The label recommends administering a single dose of 5 mg/kg (0.1 mL/kg) approximately 90 minutes before stressful events. A loading dose is not described. The product is flavored and reportedly easily accepted by cats. It may be given with a small amount of food and administered on 2 consecutive days.¹⁴ Specific drug interactions have not been documented; however, on the basis of the drug class, it is suspected that concurrent use with central nervous system (CNS) depressants may cause additional sedation.

Mechanism of Action

Pregabalin acts in the CNS by reducing release of

TABLE 1 Pharmaceuticals Commonly Used for Pretreatment of Feline Veterinary Visit Fear, Stress, and Anxiety

DRUG (CLASS)	CATEGORY	DOSE FOR BEHAVIORAL INDICATIONS	ADVERSE EFFECTS	NOTES
Gabapentin (gabapentinoid)	Analgesic (neuropathic pain), anticonvulsant, anxiolytic, sedative at higher doses	50–200 mg PO q8–12h 1.5–2 hours before event	Sedation, ataxia	- Higher doses can cause profound sedation. Responses between cats vary. 50% dose reduction advised for cats with CKD. - Some formulations may contain xylitol
Pregabalin (Bonqat; Zoetis, zoetisus.com) (gabapentinoid)	Analgesic (neuropathic pain), anticonvulsant, anxiolytic, sedative at higher doses	5 mg/kg PO; half-life 14 hours, can be given 2 consecutive days 1.5 hours before event	Mild sedation, ataxia, infrequent emesis	- More potent and longer duration of action than gabapentin - Potentially reduce dose in cats with CKD. - May affect blood pressure - Available as a flavored liquid - Schedule V controlled substance
Trazodone (serotonin antagonist/reuptake inhibitor)	Anxiolytic, sedative	50–100 mg PO 1–2 hours before event	Sedation, paradoxical excitement, GI signs	Use with caution in combination with other serotonergic drugs (e.g., SSRIs, TCAs, tramadol).
Alprazolam, lorazepam (benzodiazepines)	Anticonvulsant, anxiolytic, sedative	Alprazolam: 0.125–0.25 mg PO, 1 hour before event Lorazepam: 0.25–0.5 mg PO, 1 hour before event	Ataxia, polyphagia, disinhibition, excitation	- Use of benzodiazepines in aggressive patients is contraindicated due to potential for behavioral disinhibition. Benzodiazepines are best used with sedatives. - Unpredictable patient responses are possible, with paradoxical excitation. - Data for feline species are minimal.

CKD = chronic kidney disease; GI = gastrointestinal; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant



excitatory neurotransmitters (e.g., glutamate, norepinephrine, serotonin, dopamine, substance P, calcitonin gene-related peptide) by binding voltage-gated calcium channels at the $\alpha_2\delta$ subunit of presynaptic neurons, thereby reducing calcium influx into the cells (**FIGURE 1**). Modification of neurotransmitters is aimed at reducing fear and anxiety without sedation.¹⁴

Pharmacokinetics

Pregabalin is highly bioavailable when given orally to cats; peak plasma concentrations are achieved within 30 to 60 minutes. The drug is slowly eliminated; in healthy cats, mean half-life is 14.7 ± 2.7 hours after labeled dosing.¹⁴ The speed and degree of absorption make pregabalin more potent than its fellow gabapentinoid, gabapentin, which has a half-life of approximately 4 hours.¹² Pregabalin is minimally metabolized with hepatic methylation (<1% to 2%). The elimination route has not been specifically studied in cats, but in other species, the drug as well as its metabolites are excreted by the kidneys.¹⁴

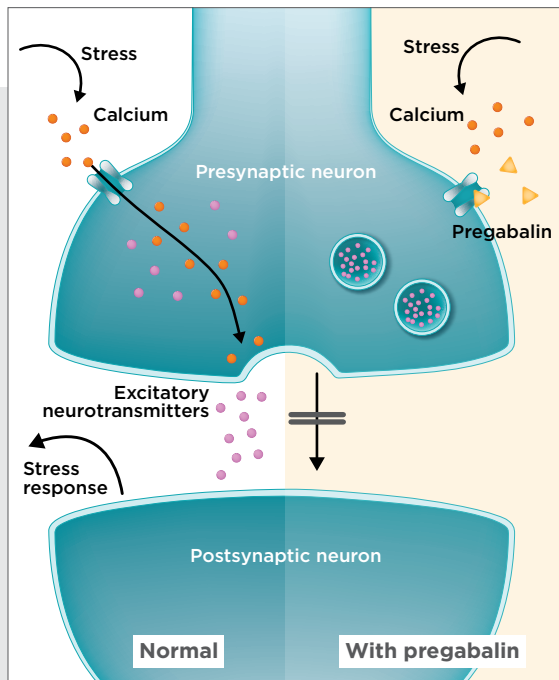


FIGURE 1. Pregabalin mechanism of action. When a cat is faced with stressful events, voltage-gated calcium channels in the presynaptic neurons allow an influx of calcium into the cells, leading to release of excitatory neurotransmitters across the synapse, resulting in a stress response. Pregabalin acts in the central nervous system by binding the voltage-gated calcium channels at the $\alpha_2\delta$ subunit, reducing calcium influx into the cells and the subsequent release of excitatory neurotransmitters, thus reducing the stress response.

Efficacy

In a blinded, placebo-controlled study of 209 cats with veterinary visit–associated anxiety, pregabalin (5 mg/kg PO) or placebo was administered by the client 90 minutes before transportation of at least 20 minutes to a routine veterinary visit, which included a complete examination and blood sampling.¹⁵ Observations of the client, examining veterinarian, and external expert reviewing recordings were documented on a 5-point numerical scale and indicated a significant decrease in travel and examination behavioral stress scores in the pregabalin-treated group. Pregabalin-treated cats were rated as showing “excellent” or “good” outcomes in 51% of client transportation experiences (versus 27% in the placebo group) and 55% of veterinary examinations (versus 30% in the placebo group). Clients noted that dosing was easy and well tolerated by their cats. A similar study using pregabalin approved for use in humans revealed poor client scores on ease of administration to their cats (presumably due to taste).¹⁶

Safety

When Bonqat was dosed according to label, the incidence of self-limiting adverse events (e.g., ataxia [4.6%], lethargy [2.8%], emesis [1.9%]) was low. The label recommends using Bonqat with caution in cats with concurrent cardiac disease or hypertension due to the potential for bradycardia and reflex hypertension noted during margin of safety study.¹⁴ In addition, caution is recommended when Bonqat is used in cats with preexisting renal disease due to its excretion; similar to gabapentin, a dose reduction may be warranted. Pregabalin safety has not been studied in cats younger than 7 months of age; breeding, pregnant, or lactating cats; or cats with severe systemic disorders.¹⁴

In margin of safety studies, pregabalin was administered to cats at doses up to 5 times the labeled dose for 6 consecutive days. The cats at the higher end of the dosing range all exhibited signs of sedation (e.g., ataxia, lethargy, recumbency, depression, mydriasis, hypothermia). Some cats experienced bradycardia and hypersalivation after dosing. Most adverse signs were self-limiting and resolved within 4 to 8 hours.¹⁴ A randomized, blinded, crossover trial of 8 healthy cats found that single doses of 5 and 10 mg/kg PO pregabalin could cause mild to moderate sedation and hypotension.¹⁷

Veterinary visits should be scheduled at the most quiet times of the day, with efforts to bring cats directly into examination rooms that are equipped with all the tools needed for the visit.

Comparison Studies

One study evaluated 50 healthy cats premedicated with intramuscular buprenorphine and either oral pregabalin (4 mg/kg) or gabapentin (10 mg/kg) in a perioperative setting in a university teaching hospital.¹⁸

Dexmedetomidine was used as a rescue agent for patients not amenable to IV catheter placement. Sedation levels and behavioral scores were collected by treatment-blinded veterinarians. Recovery time and quality were evaluated by the same veterinarians. The lack of control group did not allow for comparison of gabapentinoid-treated and nontreated cats; however, the before and after recovery variables did not differ between the gabapentin- and pregabalin-treated cats.

MULTIMODAL APPROACHES

Drugs are not the mainstay of treatment for promoting low-stress veterinary visits. Considerations must be taken by the entire team (clients included) to optimize the feline experience. Beginning at home before veterinary visits, clients should reinforce the carrier as a safe place by making it available for exploration and treat dispensing. Because drug effects vary among patients, clients should test doses of prescribed pharmaceuticals to ensure that the starting dose is ideal for their cat. Veterinary visits should be scheduled at the most quiet times of the day, with efforts to bring cats directly into examination rooms that are equipped with all the tools needed for the visit. All members of the healthcare team should use feline-friendly handling techniques.¹⁹ If levels of feline anxiety, fear, and stress are unsuitable, the anxiolytic/sedative plan should be reevaluated.

FUTURE DIRECTIONS

Use of pregabalin to manage neuropathic pain in humans, dogs, and cats has been investigated. Pregabalin for humans has been used successfully since 2005 for the treatment of fibromyalgia and other types of nerve pain.²⁰ In 46 dogs, a prospective, blinded clinical trial that investigated perioperative use of pregabalin for analgesia after intervertebral disk disease surgery found that dogs that received pregabalin 4 mg/kg PO q8h with an opioid (compared with those that received an opioid alone) exhibited a mean 2.5-unit decrease in Glasgow Composite Measure Pain Scale values.²¹ The study evaluated use of pregabalin as an adjunctive analgesic and did not allow for differentiation of the role of pregabalin in postsurgical versus neuropathic pain.

Consideration of future use of pregabalin for treatment of neuropathic pain in cats holds promise. A recent case report of a Himalayan cat suffering from orofacial pain syndrome and resultant self-mutilation describes successful treatment with pregabalin after opioids and nonsteroidal anti-inflammatory drugs failed.²² The International Society of Feline Medicine 2024 review of neuropathic pain in cats notes the potential for pregabalin as a first- or second-line option for neuropathic pain due to its potency and increased potential for client compliance with twice-daily administration. When pregabalin is used on a long-term basis, the guidelines recommend giving 2 to 10 mg/kg PO to effect and routinely monitoring bloodwork.²³ Continued study surrounding the uses of pregabalin in veterinary species is needed.

SUMMARY

Several medications are used off label for the treatment of acute feline anxiety and fear associated with transportation and veterinary visits. Pregabalin is the first U.S. Food and Drug Administration–approved flavored oral solution (Schedule V drug) that can be added to multimodal treatment for cats that associate veterinary visits with fear, anxiety, and stress. Although the cost of this drug is a consideration, pregabalin is easy to administer, potent, long lasting, and has few adverse or sedative effects at the recommended doses. While further research is needed, it also has the potential for future treatment of neuropathic pain in cats. **TVP**



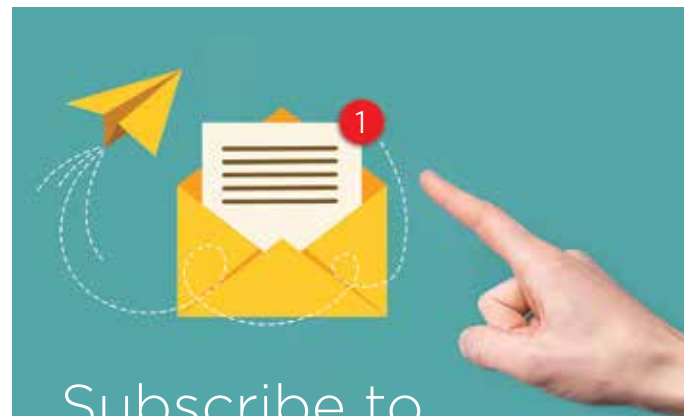
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