Comparative Study of the Physiological and Behavioral Effects of Gabapentin and Trazodone in Fractious Cats

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Abstract.
The proportional effect of a single dose of gabapentin and trazodone on calming fear- and anxiety-induced aggression in cats was examined. Twenty-seven healthy fractious DSH breed cats were randomly and double-blindly divided into three equal groups. The first group received a placebo as a control group. The second and third groups received gabapentin (22 mg kg^{-1}) and trazodone (10 mg kg^{-1}), respectively, in this study. Physiological factors (heart rate, respiration rate, systolic blood pressure, and rectal temperature) were measured after the cats were referred to the clinic. The stress level of the cats was also assessed. The sedation scores were calculated using the Feline Multiparametric Sedation Scale (FMSS). In the gabapentine group, the mean systolic blood pressure (14.05 mm Hg) and respiratory rate (26.78 breaths $minute^{-1}$) were significantly lower than in the trazodone and control groups. However, there was no statistically significant difference between the heart rate and rectal temperature groups. The mean of all behavioral factors in the trazodone and gabapentin groups was lower than that of the control group; this difference was more significant between the gabapentin and control groups. Gabapentin and trazodone administration before considering medical referral may help alleviate fear- and anxiety-induced aggression in cats. However, it's important to note that while it showed greater effectiveness in reducing physiological signs of stress, sedation may not necessarily alleviate stress itself; it could merely mask its symptoms. Gabapentin (22 mg kg^{-1}) demonstrated better efficacy in sedative effects when evaluated across various behavioral factors.

Keywords: Anxiety, Fear, Sedation, Stress, Gabapentin, Trazodone, Cat.

1. Introduction

The demonstration of fear- and anxiety-induced aggression is one of the most challenging aspects of treating companion animals, especially cats. It has been found that fractious cats, particularly those experiencing pain and disease, often exhibit aggression, which poses a significant challenge for veterinarians. Aggression is a hostile, harmful, and destructive behavior that manifests itself physically, behaviorally, and verbally. It is an adverse emotion that can hurt others or oneself (1). The origin of aggression is often associated with stress in animals. Therefore, veterinarians have employed various techniques to reduce animal stress. For example, adequate ventilation and suitable waiting and examination rooms were provided (2). Furthermore, using sedative drugs such as acepromazine, diazepam, and dexmedetomidine (3) helps reduce animal stress (4). Gabapentin, as a gamma-aminobutyric acid (GABA) analog, a vital brain neurotransmitter, is used to diminish calcium flow. From a pharmacological perspective, this drug is classified as a 1-aminomethylcyclohexaneacetic acid. However, despite being structurally similar to GABA, this drug does not interact with GABA receptors. It is not converted to GABA or its agonists after metabolism. Gabapentin has been used as an anticonvulsant medication since 1992 (5). Moreover, it is also applied to alleviate numerous forms of neuropathic pain, including diabetic neuropathy, nerve damage infection caused by herpes simplex virus (6), and reflex sympathetic dystrophy (7), as well as to prevent postoperative complications. In addition to its anticonvulsant properties, gabapentin has been found to exert sedative and anxiolytic effects by modulating the release of neurotransmitters, including norepinephrine and serotonin, in the central nervous system (8). These effects contribute to dealing with anxiety-related conditions and reducing cat stress-induced behaviors (8).

Similarly, trazodone is a weak serotonin reuptake inhibitor and a potent antagonist of serotonin receptors 5-HT_{2A} and 5-HT_{2C}. Its active metabolite is m-chlorophenylpiperazine, a 5-HT_{2C} agonist with a half-life of approximately 14 hours (9). This drug is rapidly absorbed orally, with a plasma half-life of 9-5 hours. It binds to plasma proteins approximately 95%. The drug is excreted through the bile and kidneys (9). Trazodone is used to treat depression and anxiety. It is effective in alleviating signs such as agitation, sleep disturbances, and feelings of sadness. Besides its antidepressant properties, trazodone is also commonly applied as a sedative drug (10).

Although gabapentin and trazodone have been found to possess analgesic effects (8), their comparative effects in reducing fear- and anxiety-induced aggression behaviors and responses in cats remain unclear. This study aims to compare the effectiveness of gabapentin (22 mg kg^{-1}) and trazodone (10 mg kg^{-1}) in reducing fear- and anxiety-induced aggression in fractious cats. It will assess both physiological parameters (such as heart rate and blood pressure) and behavioral factors (like sedation scores and posture). Although both medications are commonly used in veterinary practice, their relative effects on aggression related to stress have not been thoroughly explored. This study employs a double-blind, placebo-controlled design and utilizes standardized assessment tools, including the Feline Multiparametric Sedation Scale. Our goal is to provide evidence-based insights that can enhance pharmacological interventions for managing feline stress, thereby addressing an important area in clinical practice that warrants further attention.

2. Materials and Methods

2.1. Ethical Considerations

One of the primary concerns of this study is obtaining ethical approval for administering this medicine. Based on clinical evaluation, although the cats were considered healthy, they were selected for inclusion due to their fractious behavior, which warranted intervention for their welfare. Aggression in cats can have significant implications for their well-being and the safety of their owners. Thus, the administration of medications was not the only reason for research purposes, but also to address reasonable behavioral

concerns. Additionally, this study examined the comparative effects of medications for treating aggression, with the potential to inform improved treatment strategies in clinical settings. However, the welfare of the cats was prioritized throughout the study, and all procedures were conducted in accordance with ethical guidelines for the humane treatment of animals in research. The experiment was conducted in accordance with the regulations of the Iranian Society for the Prevention of Cruelty to Animals, adhering to the ethical codes for studies on laboratory animals in Iran.

2.2. Feline cases

27 domestic short-haired (DSH) cats, aged between 2 and 6 years and weighing between 2.5 and 4.5 kilograms, were included in this study. The aggressive behavior was the most selective criterion for inclusion in the study, which was assessed through standardized behavioral evaluations performed by a certified veterinary behaviorist. In addition, baseline physiological and behavioral measurements, including heart rate, respiratory rate, rectal temperature, and behavioral observations, were recorded for each cat before randomization (11). All cats also underwent thorough clinical examinations and hematological screenings to ensure they were healthy. The cats were then randomly assigned to one of three groups using a double-masked method, where neither the investigators nor the participants were aware of the group assignments. This approach aimed to minimize bias in treatment allocation and assessment, ensuring an equal distribution of cats across the groups. To reduce stress during transport and ensure their safety, the cats were transported in individual carriers. The cats were housed in calm, temperature-regulated environments for at least 8 hours to enhance their comfort and reduce anxiety. Each cat received bedding materials that were familiar to them, such as towels or blankets that carried their scent, to foster a sense of security. Their behaviors and overall health were closely monitored, and social interactions were encouraged when appropriate. Additionally, measures were taken to limit exposure to loud noises and maintain consistent feeding schedules to reduce stress further. Veterinary services were on standby to address any health issues or emergencies that might occur during the study period. In summary, significant efforts were made to safeguard the cats' well-being and lessen any possible stressors related to their transportation and care at the clinic (12).

2.3. Procedure

The cats had an initial acclimatization period of one hour to minimize stress in the various consulting rooms and achieve a suitable body posture for the investigation.

The cats were divided into three groups of nine. The first group (P) received a placebo (Empty capsule), the second group (G) was prescribed gabapentin (100 mg tablet, Abidi Company, Iran) at 22 mg kg^{-1}, and the third group (T) was administered trazodone (Trazolex 50 mg tablet, Tehran Shimi Pharmaceutical Company, Iran) at 10 mg kg^{-1}, all of which were administered three hours before the test. It was prohibited to consume food after taking the drug. The physiological factors and stress levels of cats were measured in a standardized order, followed by the following steps.

Physiological factors, including heart rate measured with a stethoscope (Littmann USA), respiratory rate measured by observing chest and abdominal movement, systolic blood pressure measured using a Doppler sphygmomanometer (Vmed vet-dop2, USA), and rectal temperature measured with a digital thermometer (Braun, Germany), were recorded in the studied cats.

The animals' stress levels were rated based on the scale presented by Kessler and Turner (1997), which comprised nine factors: body, limbs, tail, head, eyes, pupils, ears, whiskers, vocal, and activity, each ranked from 1 (very fearful) to 7 (completely calm), as described in *Table 1* (13).

The sedation scores were measured using a Feline Multiparametric Sedation Scale (FMSS). This scoring system comprises four categories: posture score, behavior, response to sound (clapping), and response to restraint and/or intramuscular injection and/or intravenous catheter. Each category was scored distinctly

on a scale from 0 to 3, where 0 indicated no sedation and 3 indicated non-responsiveness. The scores from all categories were then summed to yield a final sedation score, ranging from 0 to 12. A score of 0 represented no sedation, while a score of 12 designated maximum sedation. The sedation assessment was performed by three blinded assessors, who recorded scores both before and after administration (pre-sedation score) and 3 hours after the sedatives (post-sedation score). The final scores were compared to evaluate the effectiveness of the different treatment groups (14).

The behavior and well-being of the cats were evaluated, and modifications were made to promote their comfort and overall health. Strategies were implemented to reduce stress, including limiting handling and creating a soothing atmosphere. The cats were evaluated for three hours before being returned to their owners and were monitored for any adverse reactions. The assessment protocol focused on collecting precise data while prioritizing the welfare of the cats. All findings were documented in the appropriate forms.

Table 1. Cat stress score.

Sore	Body Position	Limbs	Tail Position	Head Position	Eye Appearance	Pupils	Ear Position	Whiskers	Vocalization	Activity
1	Lying on one side	Fully extended	Extended	Lying on the surface with chin up or face up	Closed or barely opened	Normal	Half-back	Lateral	None	Sleeping or resting
2	Ventrally laid, or half on the side, or sitting	Bent hind legs may be extended	Extended upwards or loosely downward	Laid on the surface or over the body with some movement	Closed, half-opened, or typically opened	Normal	Erected forwards or backwards	Lateral or forwards	None	Resting, alert
3	Ventrally laid or sitting	Bent (with hind legs extended)	Twitching	Over the body with some movement	Normally opened	Normal	Erected forwards or backwards	Lateral or forwards	Meow or quiet	Resting, awake
4	Ventrally laid or sitting	Bent (hind legs bent when standing)	Close to the body	Over the body with little or no movement	Wide open or pressed together	Normal or partially dilated	Erected forwards or backwards	Lateral or forwards	Meow, plaintive meow, or quiet	Cramped sleeping
5	Ventrally laid or sitting	Bent (near surface)	Wide open	On the plane of the body with less or no movement	Wide open	Dilated	Partially flattened	Lateral, forwards, or backwards	Plaintive meow, yowling, growling, or quiet	Alert may be active
6	Ventrally laid or crouched directly	Bent (near surface)	Fully opened	Near-surface, motionless	Fully opened	Fully dilated	Fully flattened	Back	Plaintive meow, yowling, growling, or quiet	Motionless or actively prowling

7	Sitting directly on all four legs	Bent	Fully opened	Lower than the body, motionless	Fully opened	Fully dilated	Entirely flattened back on the head	Back	Plaintive meow, yowling, growling, or quiet	Motionless

2.4. Statistics

GraphPad Prism version 10.4.1 was used to analyze the research data and create figures. The Kolmogorov-Smirnov test was conducted to evaluate the normality of the data distribution. The ANOVA test was employed to compare the averages among the three groups. To determine any significant differences between the means, the Tukey post-hoc test was performed with a significance threshold of $p \leq 0.05$.

3. RESULTS

3.1. Physiological Factors

Figure 1 presents the results of examining the physiological factors in fractious cats across three treatment groups: Control (Placebo), Gabapentin, and Trazodone. As observed, the mean heart rate of 170.0 beats per minute in the gabapentin group was lower than in the control group; however, this difference was not statistically significant ($p = 0.9999$). Additionally, the mean difference in body temperature between the trazodone and control groups was not statistically significant ($p = 0.9866$). Moreover, the mean difference between the two therapeutic groups was not statistically significant ($p = 0.9896$).

The mean difference in respiratory rate between the control and gabapentin groups (23.11 beats per minute) was statistically significant ($p < 0.0001$). However, the mean respiratory rate of the trazodone group (3.22 beats per minute) did not differ statistically from the control group ($p = 0.6361$). Additionally, the trazodone group had a significantly higher mean respiratory rate than the gabapentin group ($p < 0.0001$). The group receiving gabapentin exhibited significantly lower systolic blood pressure in comparison to the placebo group ($p = 0.0011$). The Trazodone group appears to lower systolic blood pressure compared to the placebo ($p = 0.0166$). No notable variations were observed among the groups in terms of rectal temperature ($p > 0.05$).

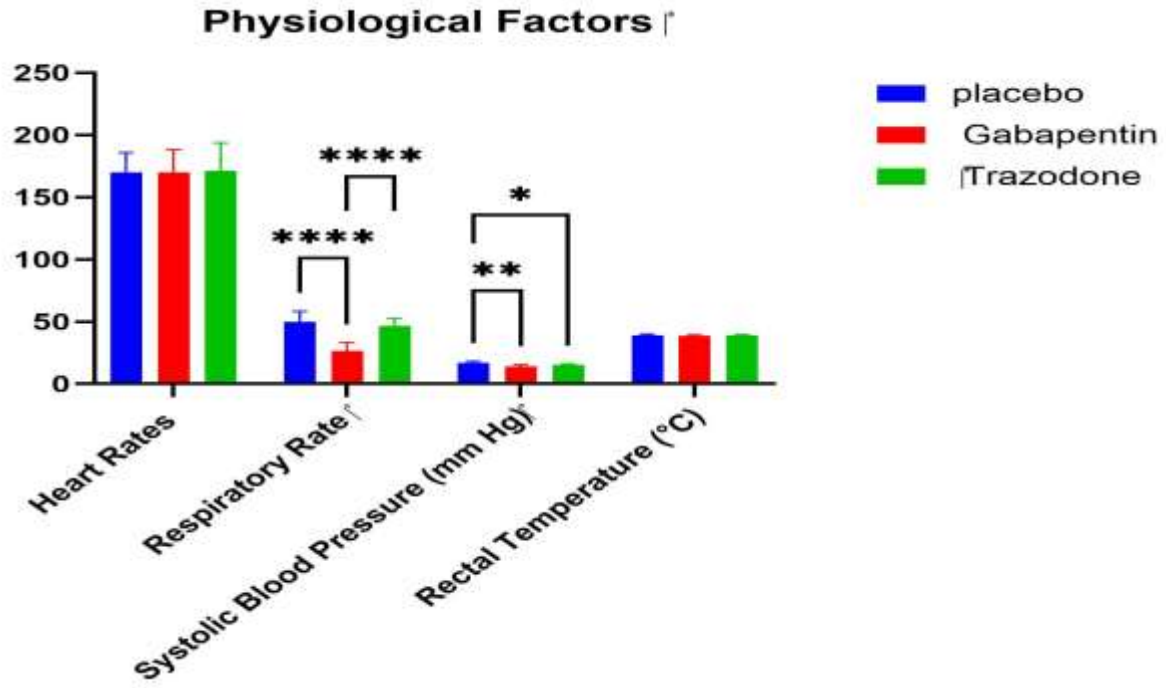

Figure 1. Comparison of Heart Rates, Respiratory Rate, Systolic Blood Pressure, and Rectal Temperature Across Control, Gabapentin, and Trazodone Treatments, with Statistical Significance Indicated (*P≤ 0.05, **P≤ 0.01, **** P≤ 0.0001).

3.2. Behavioral factors

Figure 2, which evaluates the behavioral responses of fractious cats, primarily assesses the degree of sedation induced by gabapentin and trazodone treatments ($F(4.816, 115.6) = 5.392$, $p < 0.0001$). The stress scores are based on the Kessler and Turner (1997) scale (13), with higher scores in the placebo group indicating higher stress levels. The Gabapentin group consistently shows lower stress scores across most behavioral factors than the Placebo group. The Trazodone group also tends to have lower stress scores than the Placebo group, but shows more variability. Gabapentin shows significant differences from Placebo in multiple factors, such as body position ($p < 0.0001$), limb situation ($p < 0.0001$), tail position ($p < 0.0066$), head position ($p = 0.0043$), eye appearance ($p < 0.0001$), pupils ($p < 0.0001$), ear position ($p = 0.0124$), whiskers ($p < 0.0001$), and activity ($p = 0.0359$). Trazodone also significantly improves compared to Placebo in head position ($p = 0.0150$), but appears slightly less effective than Gabapentin in certain areas. Both Gabapentin and Trazodone reduce stress compared to the control group. Gabapentin (22 mg kg^{-1}) appears to be the more practical option based on the statistically significant differences observed.

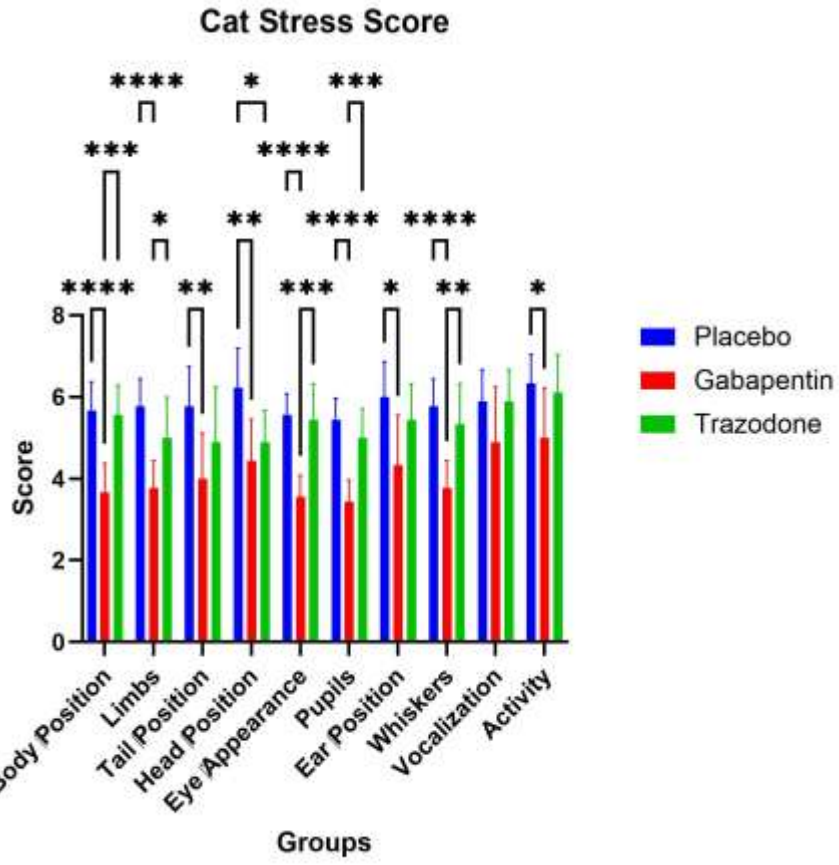

Figure 2. The behavioral factors observed in the control, gabapentin, and trazodone groups of fractious cats (*P≤ 0.05, **P≤ 0.01, ***P≤ 0.001, ****P≤ 0.0001).

3.3. Feline Multiparametric Sedation Scale

The sedation scores presented in Figure 3 are quantitative and measured on an ordinal scale ranging from 0 to 12 using FMSS, where higher scores indicate greater levels of sedation. The Figure compares pre-sedation and post-sedation scores within the gabapentin ($p < 0.0001$) and trazodone ($p < 0.0001$) groups. Additionally, the comparison of post-sedation scores among the placebo, gabapentin, and trazodone groups shows that the highest score was recorded in the gabapentin (22 mg kg^{-1}) group, which was significantly higher than the scores in the placebo ($p < 0.0001$) and trazodone ($p < 0.0001$) groups. The mean difference in post-sedation gabapentin (6 ± 1.2) versus post-sedation trazodone (2.4 ± 1.13) groups was 3.6, suggesting that gabapentin at a dose of 22 mg kg^{-1} induces more significant sedation.

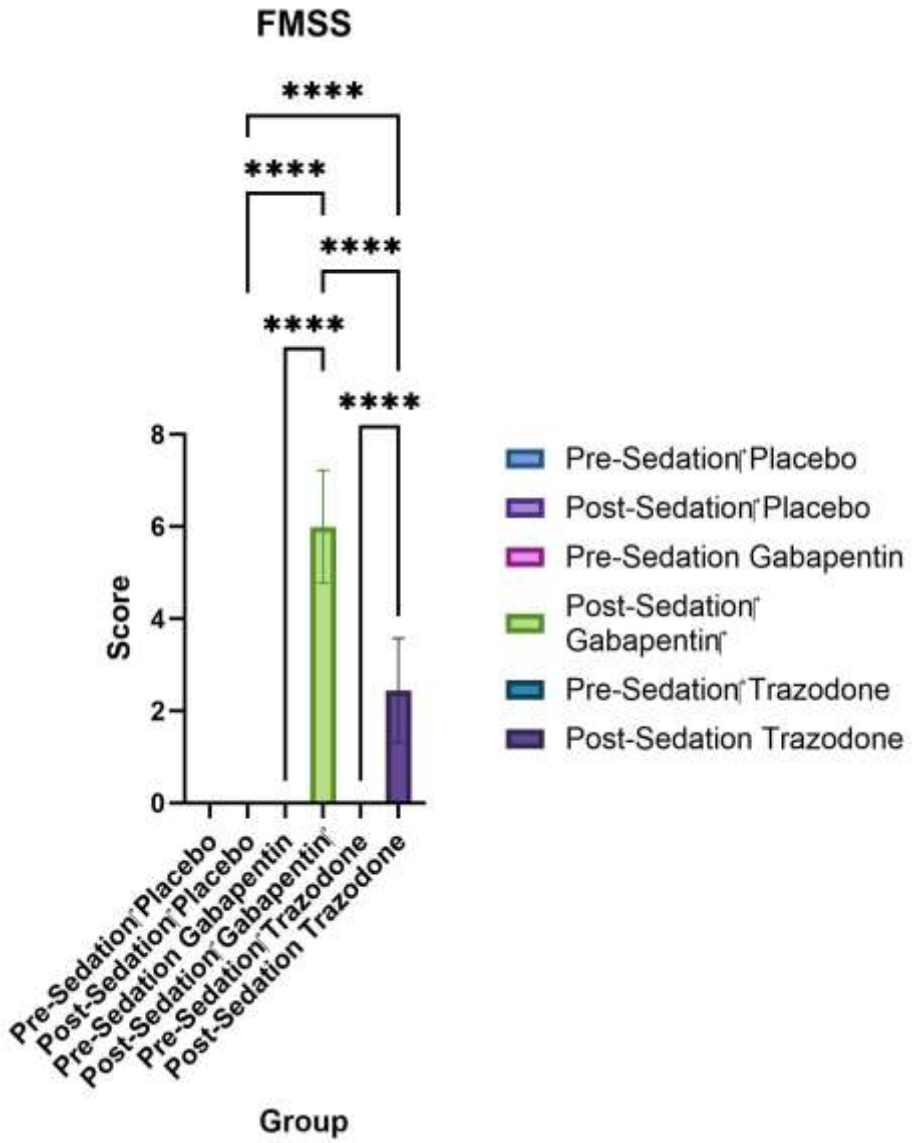

Figure 3. Comparison of Sedation Scores (FMSS) Across Treatment Groups. The figure displays the Sedation Scale (FMSS) scores, ranging from 0 (no sedation) to 12 (maximum sedation), for three treatment groups: Placebo, Gabapentin, and Trazodone. Scores were recorded before (Pre-Sedation) and 3 hours after (Post-Sedation) administration. Each bar represents the mean FMSS score, and Error bars indicate standard deviation. (****P≤ 0.0001).

4. Discussion

Many studies have been conducted to find ways to reduce fear—and anxiety-induced aggressive behavior in cats in veterinary clinics. Gabapentin and trazodone are among the medications studied for their effectiveness in lowering cats' fear and distress, as well as calming them before they are referred to veterinary clinics. Still, the comparative effect of these two drugs has not been investigated.

O'Donnell et al. demonstrated that rectal administration of trazodone (8 mg kg^{-1}) in dogs leads to relative tranquility (15). Fries et al. (2018) displayed that oral administration of trazodone (50 mg kg^{-1}) results in relaxation in cats and significantly reduces systolic blood pressure. However, it does not affect the reduction in heart rate (15). In a study similar to that of Stevens et al. (2016), the effects of oral administration of 50 mg kg^{-1} of trazodone were examined in 10 healthy but aggressive cats (16). The study found that administering the drug at the time of transfer to the hospital significantly reduced their stress and anxiety levels, but did not show any significant difference in heart rate or other physiological parameters (16). In the present study, a lower dose of trazodone was used, yielding similar results. Therefore, the use of lower doses can have similar effects.

Furthermore, some studies using higher doses than those in the present study have also achieved similar results. For example, Orlando et al. (2015) examined the effects of 50, 75, and 100 mg doses in referred cats to veterinary clinics and found that all doses induced calmness in the animals (17). As mentioned earlier, a single dose was used in this study, and we saw calmness in the patients. Therefore, the creation of calmness is not dose-dependent. In other studies, such as Gruen et al. (2008), the effects of long-term trazodone use on controlling animal aggression have also been investigated, yielding similar results (18). This study also demonstrated that trazodone effectively reduced fear- and anxiety-induced aggression behaviors in cats, as evidenced by behavioral, physical, and hematologic data (CBC and serum biochemical panel) results.

Gabapentin is one of the drugs that effectively reduces cats' stress and fear before referral to veterinary centers. Veronezi et al. (2022) found in their investigation that oral administration of gabapentin (100 mg/cat) in fractious cats leads to an improvement in cardiac status, as indicated by both heart rate and echocardiographic findings (19). In the current study, Gabapentin and Trazodone influence certain physiological factors in fractious cats. Gabapentin significantly reduces systolic blood pressure, while Trazodone leads to a notable increase in respiratory rate. Heart rate and rectal temperature remain relatively unchanged across the groups. In another study, Van Haaften et al. (2017) investigated the effect of administering oral doses ranging from 4.29 to 13 mg kg^{-1}. A 100 mg dose of gabapentin reduced the respiratory rate by 2.15 breaths per minute. They claimed that this reduction may be due to the drug's effect on the sympathetic axis (25). In this study, gabapentin also decreased the respiratory rate.

Pankratz et al. (2017) investigated the effects of oral gabapentin administration at two doses: 10 and 50 mg. They also found that the stress score in the gabapentin-receiving groups was significantly lower than that of the control group. According to them, the most significant reduction was observed in the first two hours after drug injection (20).

Furthermore, Ghanaee et al. (2012) demonstrated that gabapentin could reduce pain and induce calmness in patients after reproductive surgeries (21). In this study, gabapentin demonstrated better effectiveness and safety when evaluated across various behavioral factors, including body, limb, tail, head, eyes, pupils, ears, whiskers, vocalization, and activity levels.

However, there are studies whose results differ from those of the current study. For example, Wagner et al. (2010) found in their research, which investigated the analgesic effects of gabapentin (10 mg kg^{-1}) in dogs, that drug administration did not reduce stress (22). The differences between the findings of this study and those of the present study may be due to variations in the study conditions and the population under investigation. The present study examined the sedative effects on healthy fractious cats. In another study, researchers investigated the sedative effects of a medication on dogs after limb surgery.

The present study demonstrated that the number of heartbeats decreases after consuming gabapentin. Van Haaften et al. (2017) also obtained similar results, showing a decrease of 2.15 beats per minute, which, according to them, is not clinically significant (23).

Y Wu et al. (2025) investigated the effects of oral trazodone administered at doses of 50 mg, 75 mg, and 100 mg on sedation, physiological parameters, and echocardiographic evaluations in healthy cats. The findings revealed that trazodone induced mild sedation without causing muscle relaxation or pain relief. Furthermore, it led to only slight alterations in systolic blood pressure, pulse rate, and respiratory rate, and had no significant effect on echocardiographic measurements. These results confirm the safe administration of oral trazodone as a mild sedative for cats in clinical environments, as it does not negatively impact cardiovascular function at the studied doses (10).

Laura E Tucker et al. (2024) revealed oral trazodone (5 mg kg^{-1}) and the trazodone/gabapentin combination significantly sedated healthy cats compared to gabapentin (10 mg kg^{-1}), with no significant side effects. The degree of sedation was increased when the trazodone/gabapentin combination was administered, and a gabapentin dose of 10 mg kg^{-1} alone was unsuccessful in providing significant sedation (14). In our study, gabapentin at a 22 mg kg^{-1} dose proved to be the most effective sedative, producing significant sedation across all measured parameters in fractious cats. Trazodone at a dose of 10 mg kg^{-1} provides moderate sedation, but not as strong as Gabapentin.

EC Siepmann et al. (2025) investigated the sedative and physiological effects of oral trazodone and gabapentin, alone or combined, in healthy cats. The combination of trazodone (50 mg) and gabapentin (100 mg) produced higher sedation scores than either drug alone, with mild impacts on heart rate, respiratory rate, blood pressure, and isovolumetric relaxation time, but no significant alterations in hematological, biochemical, or electrocardiographic parameters. These results suggest the trazodone-gabapentin association is effective in enhancing sedation with minimal cardiovascular or systemic adverse effects in feline patients (24).

The results of this study indicate that trazodone and gabapentin both effectively alleviate stress in cats before their referral to the treatment center. When compared to a placebo, both medications are more effective at decreasing anxiety, principally under challenging situations. Gabapentin, in particular, shows a more reliable and significant decrease in stress across various behavioral aspects. This study had several drawbacks. One drawback was the limited number of participants, which may have hindered the ability to achieve more extensive findings in future research involving larger groups. Another limitation was that the study focused on healthy cats, suggesting that different outcomes might occur in cats with illnesses.

In conclusion, a single dose of gabapentin (22 mg kg^{-1}) or trazodone (10 mg kg^{-1}) significantly reduces fear- and anxiety-induced aggression in fractious cats. Our results suggest that gabapentin may be the preferred option for managing stress in these cats, although trazodone also provides benefits. Overall, these findings indicate that gabapentin could serve as an effective pre-visit sedative for fractious cats.

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Authors' Contributions

1- Acquisition of data: A. R. A. N.
2- Analysis and interpretation of data: N. P. and F. A.
3- Drafting of the manuscript: A. R. A. N.
4- Critical revision of the manuscript for important intellectual content: N. P. and F. A.
5- Statistical analysis: N. P.
6- Administrative, technical, and material support: A. R. A. N.
7- Study supervision: N. P. and F. A.
8- All authors reviewed and approved the final manuscript.

Conflict of Interests

The authors declare that they have no conflict of interest.

Ethics Approval

The study was approved by the Ethics Committee of Science and Research Branch, Islamic Azad University (Approval date: 06.03.2023; Approval Number: IR.IAU.SRB.REC.1400.197). All animal procedures were conducted in accordance with the ethical standards and the principles outlined in the Helsinki Declaration, ensuring the welfare of the animals.

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Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declaration of Generative Artificial Intelligence (AI)

The authors declare that the article, as well as the tables and figures, were not written/created using AI or AI-assisted technologies.

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