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Original Article

Behavioral and physiological effects of gabapentin and its combination with trazodone in aggressive domestic cats

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ABSTRACT

Stress and aggression in cats, particularly during veterinary visits, present significant challenges for both clinicians and pet owners. This study aimed to evaluate the physiological and behavioral effects of gabapentin alone and in combination with trazodone in managing stress-induced aggression in domestic short-haired cats. Twenty-seven cats were randomly assigned to three groups: placebo, gabapentin (5 mg/kg), and gabapentin (5 mg/kg) combined with trazodone (10 mg/kg). Physiological factors, including heart rate, respiratory rate, systolic blood pressure, and rectal temperature, as well as behavioral factors such as posture, vocalization, and activity levels, were assessed. The results revealed that the combination therapy significantly reduced respiratory rate and rectal temperature compared to gabapentin and placebo ($p \leq 0.05$), highlighting its enhanced ability to modulate physiological stress responses. Behavioral assessments showed substantial improvements in the gabapentin + trazodone group, with reductions in fear-driven behaviors, indicating a synergistic effect of the combination. The gabapentin-only group demonstrated moderate improvements over placebo, confirming its efficacy as a standalone treatment. This study underscores the clinical benefits of combining gabapentin and trazodone for managing feline stress and aggression. The findings suggest that this protocol offers a practical and effective solution for high-stress scenarios, such as veterinary visits, enhancing animal welfare.

اثرات رفتاری و فیزیولوژیکی گاباپنتین و ترکیب آن با ترازودون در گربه های اهلی پرخاشگر

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چکیده

استرس و پرخاشگری در گربه ها، به ویژه در زمان معاینه دامپزشکی، چالش های مهمی را برای پزشکان و صاحبان حیوانات خانگی ایجاد می کند. این مطالعه با هدف بررسی اثرات فیزیولوژیکی و رفتاری گاباپنتین به تنهایی و در ترکیب با ترازودون در مدیریت پرخاشگری ناشی از استرس در گربه‌های مو کوتاه اهلی انجام شد. بیست و هفت گربه به طور تصادفی به سه گروه دارونما، گاباپنتین و گاباپنتین همراه با ترازودون تقسیم شدند. عوامل فیزیولوژیک، از جمله ضربان قلب، تعداد تنفس، فشار خون سیستولیک و دمای رکتوم، و همچنین عوامل رفتاری مانند وضعیت بدن، صدا و سطح فعالیت مورد بررسی قرار گرفتند.نتایج نشان داد که درمان ترکیبی به طور قابل‌توجهی میزان تنفس و دمای رکتوم را در مقایسه با گاباپنتین و دارونما کاهش می‌دهد ($p \leq ۰/۰۵$)، که بر توانایی آن برای تعدیل پاسخ‌های استرس فیزیولوژیکی تاکید می‌کند. ارزیابی های رفتاری بهبودهای قابل توجهی را در گروه گاباپنتین + ترازودون نشان داد که با کاهش رفتارهای ترس محور همراه بود و نشان دهنده اثر هم افزایی این ترکیب است. گروهی که فقط گاباپنتین مصرف می‌کردند نسبت به دارونما پیشرفت‌های متوسطی را نشان دادند که اثربخشی آن را به عنوان یک درمان مستقل تأیید کرد.این مطالعه بر مزایای بالینی ترکیب گاباپنتین و ترازودون برای مدیریت استرس و پرخاشگری گربه ها تاکید می کند.

واژه های کلیدی: گاباپنتین، ترازودون، پرخاشگری گربه، مدیریت استرس، رفتار شناسی دامپزشکی

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INTRODUCTION

Managing feline aggression, especially during veterinary visits, is a significant challenge for pet owners and veterinarians. Triggered by fear, anxiety, or pain, this aggression can risk caregiver safety and compromise medical care, as resistant cats make exams or procedures difficult. Addressing this is crucial for both feline well-being and maintaining a safe care environment. Despite recent advances, effective strategies to reduce feline aggression are still greatly needed [1-3]. Pharmacological interventions have become central to mitigating stress-induced aggression in cats. Among these, gabapentin stands out as a widely used sedative and anxiolytic. Gabapentin, a gamma-aminobutyric acid (GABA) analog, modulates calcium channels in neuronal cells, reducing excitability and promoting sedation [4]. Its primary advantage lies in its ability to reduce anxiety and aggression with minimal side effects, making it a preferred choice for pre-visit sedation [5, 6]. Furthermore, gabapentin has demonstrated effectiveness in alleviating stress-related physiological responses, including elevated heart and respiratory rates, which are commonly observed in aggressive cats [7-9]. These attributes have solidified gabapentin's role as a cornerstone in managing feline stress [10]. Trazodone, another agent used in veterinary practice, complements gabapentin via its action on serotonin receptors to promote relaxation and reduce anxiety [11, 12], offering both sedation and stress relief [13, 14]. Studies indicate its effectiveness against feline aggression during stressful events, with rapid absorption and limited side effects supporting its use for short-term management [15-17]. Additionally, its rapid absorption and minimal adverse effects make it a viable option for short-term stress management in cats [16-18]. Despite the demonstrated benefits of gabapentin and trazodone, there remains a gap in understanding the potential advantages of using these two drugs in combination. While gabapentin targets neural excitability, trazodone modulates the serotonergic system, suggesting the potential for synergistic effects when combined [15, 19]. Combination therapy could theoretically enhance stress reduction by addressing multiple pathways involved in fear and anxiety [15]. This approach may offer a more effective solution for managing feline aggression, especially in high-stress environments like veterinary clinics.

The aim of this study is to compare the physiological and behavioral effects of gabapentin alone versus a gabapentin-trazodone combination in aggressive domestic cats, to identify an optimal pharmacological protocol for stress and aggression management in clinical settings. We hypothesize that the combination of gabapentin and trazodone will result in enhanced sedation and reduced aggression compared to either drug administered alone, without significant adverse effects [20]. By focusing on key physiological indicators, such as heart and respiratory rates, alongside behavioral markers, including posture, tail movement, and vocalization, this research seeks to provide evidence-based insights to improve clinical practices for managing stress and aggression in feline patients.

MATERIALS AND METHODS

Study Design and Animals

This study involved a cohort of 27 aggressive domestic short-haired (DSH) cats, comprising 15 males and 12 females, aged 2 to 6 years and weighing between 2.5 and 4.5 kilograms. The cats were chosen based on aggressive behaviors identified through standardized assessments conducted by an experienced veterinary behaviorist. These assessments ensured that

only cats exhibiting aggression were included, while maintaining a healthy status verified through clinical evaluations. To minimize confounding variables, demographic characteristics such as age, sex, neuter status, and breed distribution were carefully documented and analyzed. The study ensured an equitable mix of sexes (male and female), neutered and intact individuals, and diverse breeds, avoiding overrepresentation of any single category. This balance helped to ensure the observed outcomes were attributable to the interventions rather than inherent demographic differences. Participant recruitment was conducted through veterinary clinics, pet-related businesses, and online platforms dedicated to pet care. Interested owners received detailed information regarding the study's goals and procedures. After providing consent, owners attended an initial consultation in which they completed a thorough questionnaire about their cats' health, behavior, and environment. This preliminary data collection formed the basis for assigning cats to treatment groups in a randomized, double-blind manner to minimize bias. To gather behavioral data, the study used the validated mini–Feline Behavioral Assessment and Research Questionnaire (mini-FE-BARQ). This 42-item questionnaire enabled owners to provide detailed observations of their cats' behavior over the preceding week, focusing on body posture, tail movements, vocalizations, and overall activity levels. The responses established a quantitative baseline for evaluating the impact of gabapentin and the gabapentin-trazodone combination on aggression and stress. Statistical analysis of these responses allowed for a clear comparison of the drugs' effectiveness. To ensure accuracy, owners were given clear instructions for completing the mini-FE-BARQ and were introduced to a standardized Body Condition Score (BCS) system. Accompanied by detailed descriptions and illustrative images, this system allowed owners to reliably assess their cats' body condition. During veterinary visits, trained professionals conducted independent assessments, providing a secondary evaluation to validate the owners' input. Before any treatments were administered, baseline physiological and behavioral measurements, including heart rate, respiratory rate, and rectal temperature, were recorded. Clinical examinations and laboratory tests, including hematological screening, confirmed the cats' health status. Following these evaluations, the cats were assigned to three treatment groups—control, gabapentin, and gabapentin-trazodone—using a double-blind randomization process to ensure unbiased allocation. Transportation and housing conditions were meticulously managed to reduce stress. Each cat was transported in an individual carrier to the clinic and housed in a quiet, temperature-controlled room. Familiar bedding materials, such as towels carrying the cat's scent, were provided to foster security. Veterinary staff closely monitored the cats, using enrichment activities and maintaining consistent feeding schedules to promote comfort. All necessary precautions were taken to address potential medical concerns or emergencies promptly.

Study Protocol

Upon arrival at the clinic, the cats were given an hour-long acclimatization period to reduce stress and allow them to adapt to the environment. Each cat was placed in a separate consultation room to encourage relaxed postures suitable for observational studies. This preparatory step aimed to ensure accurate data collection by minimizing stress-induced variability in behavior and physiological responses. The cats were randomly assigned to one of three groups, each consisting of nine individuals. The first group served as the control

and received an orally administered placebo in the form of an empty capsule. The second group was given gabapentin (manufactured by Abidi Company, Iran) at a dose of 5 mg per kg, administered orally. The third group received a combination of gabapentin (5 mg per kg) and trazodone (Chemical Pharmaceutical Company, Iran) at a dose of 10 mg per kilogram of body weight, administered together orally. All medications were given three hours prior to the cats' arrival at the clinic [21]. The dosage for each cat was meticulously calculated based on its weight and medical history to ensure both safety and efficacy. Owners were instructed to withhold food from their cats for 1 hour after administering the medication to prevent potential interference with drug absorption. Once medicated, the cats were transported to the clinic by their owners, where they underwent an additional hour of acclimatization upon arrival to further minimize stress. Following acclimatization, standardized measurements of physiological factors, including heart rate, respiratory rate, systolic blood pressure, and rectal temperature, were conducted. Heart rate was recorded using a Littmann Classic III stethoscope (USA), respiratory rate was determined by observing chest and abdominal movements, systolic blood pressure was measured with a Contec 08A-Vet Doppler sphygmomanometer (Germany), and rectal temperature was obtained using a Chicco 9050 digital thermometer (Iran). These measurements were performed in a consistent order to ensure reliability across all groups. Behavioral assessments were conducted using the mini-FE-BARQ questionnaire, completed by cat owners both before and after the clinic visit. This tool

Table 1: Cat stress score.

Score	Body Position	Limbs	Tail Position	Head Position	Eye Appearance	Pupils	Ear Position	Whiskers	Vocalization	Activity
1	Laid on one side	Fully extended	Extended	Laid on the surface with chin up or on the surface	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 normally opened	Normal	Erected forwards or backwards	Lateral or forwards	None	Resting, alert
3	Ventrally laid or sitting	Bent (with hind legs extended)	Twitching	Over 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 body	Over 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 openned	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	Fully flattened back on head	Back	Plaintive meow, yowling, growling, or quiet	Motionless

provided a thorough evaluation of behavioral changes by analyzing factors including body posture, tail position, vocalizations, and activity levels. The results quantified the impact of the medications on aggression and stress-related behaviors.

To evaluate stress levels, the cats were scored on a scale adapted from Kessler and Turner (1997). This scale examined nine specific parameters, including body position, limb movements, tail positioning, head orientation, eye appearance, pupil dilation, ear posture, whisker orientation, and vocalization. Each parameter was rated on a scale from 7 (highly fearful) to 1 (completely calm), providing a detailed behavioral profile for each cat (Table 1). Veterinary staff closely monitored the cats throughout the assessment, employing stress-reducing measures such as minimal handling and a quiet, calming environment. The entire evaluation process, including physiological and behavioral assessments, lasted approximately three hours, after which the cats were returned to their owners. Veterinary professionals also monitored the cats for any adverse reactions during this period. All data were meticulously recorded using standardized forms to ensure accuracy and consistency throughout the study.

Statistical Analysis

Data analysis was conducted using SPSS version 25. The normality of the data distribution was evaluated using the Kolmogorov-Smirnov test to determine whether parametric or non-parametric tests were appropriate. For comparisons between the three groups, a one-way analysis of variance (ANOVA) was performed. Post hoc analyses were conducted using the Tukey test to identify significant differences between groups, with a significance threshold of $p \leq 0.05$. In addition, the study assessed demographic variables, including breed, age, sex, and neuter status, to confirm homogeneity across groups. This step aimed to minimize potential confounding factors and ensure that observed effects were attributable to the treatments rather than to demographic differences.

RESULTS

Demographic factors

An analysis of age, weight, breed, sex, and neuter status was conducted across the placebo, gabapentin, and gabapentin + trazodone groups to assess demographic balance. The results showed no statistically significant differences among the groups ($p > 0.05$), confirming that the allocation was evenly distributed. The cats ranged in age from 2 to 6 years, with weights ranging from 2.5 to 4.5 kilograms. The sex distribution and neuter status were also comparable across the groups, with similar proportions of male and female cats and of neutered and intact individuals. Additionally, the breeds represented were diverse and evenly distributed, ensuring no overrepresentation of specific genetic traits or behavioral predispositions. These findings indicate that the groups were demographically comparable, minimizing the risk of bias or confounding due to population characteristics. This uniformity strengthens the study's validity by ensuring that observed outcomes were more likely due to the interventions rather than to underlying demographic differences.

Behavioral factors

The cats' behavioral responses were evaluated using metrics including body posture, tail movement, vocalizations, and activity levels. The gabapentin + trazodone group demonstrated

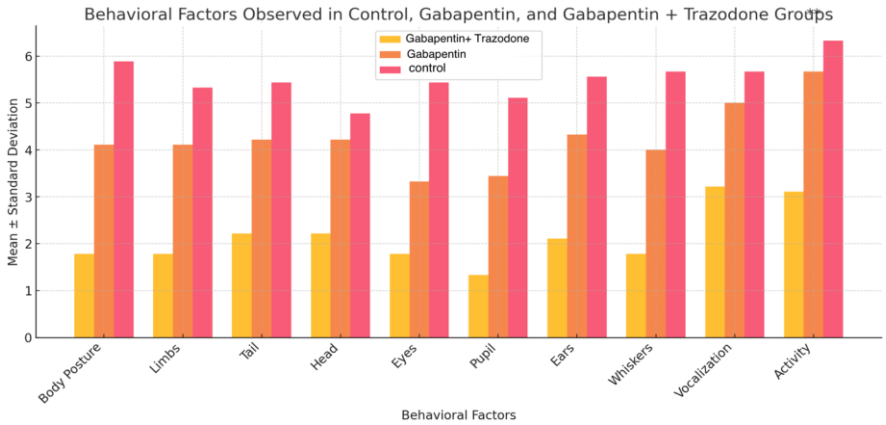

Figure 1: Behavioral factors observed in the control, gabapentin, and gabapentin + trazodone groups of aggressive cats.

Table 2: Mean ± Standard Deviation of Behavioral Factors in the Control, Gabapentin, and Gabapentin + Trazodone Groups of Aggressive Cats

Group	Body Posture	Limbs	Tail	Head	Eyes	Pupil	Ears	Whiskers	Vocalization	Activity
Gabapentin + Trazodone	1.78 ± 0.83**	1.78 ± 0.83**	2.22 ± 1.09**	2.22 ± 0.83	1.78 ± 0.66**	1.33 ± 0.50**	2.11 ± 1.36**	1.78 ± 0.83**	3.22 ± 1.64**	3.11 ± 1.26**
Gabapentin	4.11 ± 1.05	4.11 ± 0.92	4.22 ± 1.30*	4.22 ± 1.09	3.33 ± 0.70	3.44 ± 0.72*	4.33 ± 1.22*	4.00 ± 0.70*	5.00 ± 1.22*	5.67 ± 1.00*
Control	5.89 ± 0.78	5.33 ± 1.11	5.44 ± 1.33	4.78 ± 0.83	5.44 ± 0.88	5.11 ± 0.60	5.56 ± 0.88	5.67 ± 1.00	5.67 ± 0.86	6.33 ± 0.70

*: Statistically significant compared to the Control group (*p≤ 0.05).

: Statistically significant compared to both the Control and Gabapentin groups (p≤ 0.001).

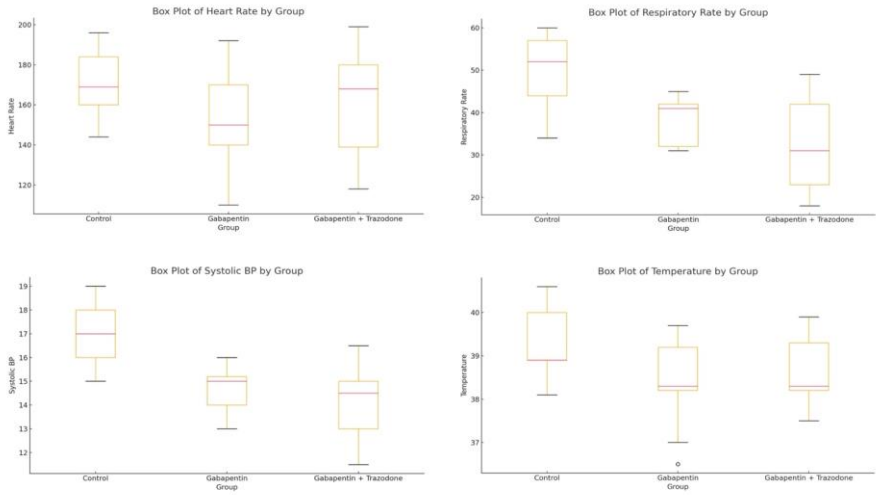

Figure 2: Box plots of heart rate, respiratory rate, systolic blood pressure, and rectal temperature across Control, Gabapentin, and Gabapentin + Trazodone groups.

Table 3: Mean ± Standard Deviation of Behavioral Factors in the Control, Gabapentin, and Gabapentin + Trazodone Groups of Aggressive Cats

Group	Heart Rate (beats/min)	Respiratory Rate (breaths/min)	Systolic Blood Pressure (mmHg)	Rectal Temperature (¬∞C)
Control (Placebo)	179.33 ± 27.91	38.22 ± 8.09	147.67 ± 49.51	39.04 ± 0.87
Gabapentin	154.33 ± 18.04	33.78 ± 7.04*	157.22 ± 19.86	39.06 ± 0.76
Gabapentin + Trazodone	144.11 ± 28.51	21.33 ± 4.39**	140.56 ± 16.85	38.71 ± 0.66*

*: Statistically significant compared to the Control group (*p≤ 0.05).

: Statistically significant compared to both the Control and Gabapentin groups (p≤ 0.001).

the greatest improvement in behavioral parameters compared with the gabapentin-only and placebo groups. These findings suggest that the combination therapy was more effective at alleviating stress-induced behavioral changes (Figure 1). The mean scores for behavioral factors were consistently higher in the gabapentin + trazodone group across all measured categories, indicating greater relaxation and reduced aggression. For instance, changes in body posture and tail position — key indicators of stress and agitation — were more pronounced in this group. Similarly, reduced vocalizations and calmer activity levels were observed, reflecting a stronger calming effect than in the other two groups (Table 2). In contrast, the gabapentin group demonstrated moderate improvements in behavior, with scores surpassing the placebo group but not as markedly as those of the combination therapy group. The placebo group showed the least change, with behaviors remaining largely consistent with baseline assessments, underscoring the efficacy of pharmacological intervention for stress reduction. Statistical analysis revealed significant differences in behavioral scores between the gabapentin + trazodone and placebo groups ($p \leq 0.05$) in most categories, particularly measures related to relaxation, such as body posture and vocalization. While the gabapentin group also showed improvements compared with placebo, the differences were less pronounced.

Physiological factors

The physiological parameters—heart rate, respiratory rate, systolic blood pressure, and rectal temperature—were evaluated to determine the effects of the treatments. The group receiving gabapentin combined with trazodone showed the greatest reductions in heart and respiratory rates compared with the gabapentin-only and placebo groups. Although the heart rate reductions were not statistically significant ($p > 0.05$), the mean heart rate in the gabapentin + trazodone group was 144.11 beats per minute, compared to 154.33 in the gabapentin group and 179.33 in the placebo group. Respiratory rate declined significantly in the gabapentin + trazodone group, to a mean of 21.33 breaths per minute. This was significantly lower than both the gabapentin group (33.78 breaths per minute) and the placebo group (38.22 breaths per minute) ($p \leq 0.05$), highlighting the superior efficacy of the combination therapy in reducing stress-related respiratory changes (Figure 2). Rectal temperature measurements also differed significantly between the groups. The gabapentin + trazodone group had a mean rectal temperature of 38.71°C, which was lower than both the gabapentin group (39.06°C) and the placebo group (39.04°C) ($p \leq 0.05$). Conversely, systolic blood pressure did not differ significantly among the groups, with averages of 140.56 mmHg in the gabapentin + trazodone group, 157.22 mmHg in the gabapentin group, and 147.67 mmHg in the placebo group (Table 3).

DISCUSSION

This study highlights the significant potential of combining gabapentin and trazodone for managing stress and aggression in cats, showing superior results compared to gabapentin alone or placebo. The physiological responses, including heart rate, respiratory rate, and rectal temperature, revealed that the combination therapy provided better modulation of stress-related changes. These findings support the broader understanding of trazodone's serotonergic effects, which have been shown to complement gabapentin's action on neuronal calcium channels. For example, a study by

Orlando et al. (2015) demonstrated that trazodone effectively induced calmness in cats at various doses, which is consistent with the significant reductions in respiratory rate observed in this study [17]. Additionally, while Van Haaften et al. (2017) noted that gabapentin alone could reduce respiratory rate, the present study shows that combining it with trazodone yields significantly greater effects, likely due to the dual pathways targeted by the combination [6]. Behaviorally, cats receiving the combination therapy showed greater reductions in stress indicators, including changes in body posture, vocalizations, and hyperactivity. These results align with those of Stevens et al. (2016), who found that trazodone alone significantly reduced anxiety in cats during veterinary visits, thereby improving handling and transportation experiences [13]. However, our study suggests that the combination of gabapentin and trazodone may offer even greater benefits by reducing both fear-driven physiological arousal and observable behavioral signs of stress. Pankratz et al. (2018) reported moderate success with gabapentin in reducing fear responses in cats, particularly in community settings, but the addition of trazodone appears to amplify these effects [8]. This synergistic effect is particularly important for clinical environments, where managing fear and aggression is critical for the safety of both the animal and the veterinary staff. Interestingly, the results from the gabapentin-only group in this study showed moderate improvements, consistent with previous research identifying gabapentin as an effective standalone anxiolytic. Veronezi et al. (2022) demonstrated that gabapentin improved cardiac parameters and reduced stress indicators, albeit with some limitations [7]. However, gabapentin's reliance on calcium channel modulation alone may not fully address the broader neurochemical mechanisms underlying severe stress responses, as suggested by studies such as Fries et al. (2019), which highlighted trazodone's ability to modulate serotonin pathways [16]. This explains why the gabapentin + trazodone group in our study outperformed the gabapentin group, as the combination leverages complementary mechanisms to achieve a more robust anxiolytic effect. The placebo group in our study provided a valuable baseline for comparison, with minimal changes observed in either physiological or behavioral factors. This finding reinforces the limited efficacy of non-pharmacological interventions in managing acute stress and aggression in cats. Similar trends were observed in studies such as Tucker et al. (2023), in which untreated groups failed to show significant reductions in stress markers [15]. These results emphasize the importance of pharmacological strategies for managing feline aggression, particularly in high-stress settings like veterinary visits. While environmental modifications, such as quiet housing and familiar bedding, can provide supportive benefits, they are unlikely to match the efficacy of targeted drug therapies. The results also offer insights into the dosing strategies for trazodone and gabapentin. Our study utilized a dose of 10 mg/kg for trazodone in combination with 5 mg/kg of gabapentin, which proved effective in achieving significant reductions in stress-related parameters. Comparatively, Orlando et al. (2015) examined higher doses of trazodone and reported similar calming effects [17]. The consistency of results across different dosing ranges suggests that trazodone may be effective at lower doses when used alongside gabapentin, offering a practical and safe protocol for clinical use. Furthermore, the findings align with those of Stevens et al. (2016), who reported that trazodone improved behavioral scores at comparable doses during veterinary visits [13]. The behavioral improvements observed in this study, particularly in the gabapentin + trazodone group, were more pronounced than those reported in prior studies involving single-drug

protocols. For instance, Pankratz et al. (2018) noted significant reductions in fear-driven behaviors with gabapentin, but these improvements were not as extensive as those achieved with combination therapy in the current study [8]. This highlights the added value of addressing multiple neurochemical pathways, as trazodone's serotonin modulation complements gabapentin's action on neuronal excitability. Moreover, the combination therapy's ability to produce consistent improvements across a wide range of behavioral factors underscores its versatility and efficacy in managing complex stress responses in cats. Siepmann et al. (2023) and the present study both evaluate the combined effects of trazodone and gabapentin in cats, emphasizing their sedative and physiological impacts. Siepmann et al. (2023) focused on healthy cats and reported that the combination significantly increased sedation scores compared to either drug alone, with mild reductions in heart rate (HR), respiratory rate (RR), and systolic blood pressure (SBP), alongside a slight increase in isovolumetric relaxation time (IVRT). Similarly, our study demonstrated that the combination reduced HR and RR more effectively than single-drug treatments, aligning with their findings. However, while Siepmann et al. (2023) emphasized cardiovascular parameters such as IVRT and systolic function, our work focused on behavioral stress reduction during veterinary handling in aggressive cats, providing a more practical application of the drug combination in clinical settings. Both studies highlight the additive benefits of trazodone and gabapentin, but with differing emphases on physiological versus behavioral outcomes [20]. While the findings of this study are promising, they also highlight several important limitations that warrant consideration in future research. First, the single-dose design restricts the findings to short-term effects, and the crossover trial design, despite incorporating washout periods, may have introduced carryover effects. Second, the absence of plasma drug concentration measurements limits the ability to precisely correlate drug levels with observed sedation and physiological effects. Additionally, although all cats in this study were adults, the lack of a fully standardized age range may have contributed to variability in behavioral and physiological outcomes. Similarly, sex-based behavioral differences were not explicitly analyzed, which may have influenced the results. Future research should consider stratified analyses by sex to better account for this variability. Finally, although this study included a 2-month follow-up to monitor potential complications, long-term studies are needed to evaluate the repeated use of gabapentin and trazodone in cats. Exploring the mechanisms underlying the observed synergistic effects could also provide valuable insights into optimizing dosing strategies and expanding the clinical applications of these drugs. Larger-scale studies involving more diverse feline populations are necessary to validate these findings and establish comprehensive guidelines for their use in veterinary practice.

CONCLUSION

This study aimed to evaluate the effectiveness of a gabapentin and trazodone combination therapy for managing stress and aggression in cats, providing a clinically relevant solution for high-stress situations such as veterinary visits. The results demonstrate that this combination outperforms both gabapentin alone and placebo by significantly reducing physiological stress markers, such as respiratory rate and rectal temperature, and by improving behavioral indicators, such as body posture and activity levels. By leveraging complementary neurochemical pathways, this approach provides a robust pharmacological strategy to reduce

stress and aggression in feline patients. These findings contribute to the growing body of evidence supporting the clinical utility of combination therapies in veterinary medicine and offer valuable insights for practitioners seeking effective stress-management solutions. However, further research is warranted to assess the long-term safety, optimize dosing strategies, and explore broader applications of this therapy in other stress-inducing scenarios. This study provides a strong foundation for advancing feline behavioral medicine and enhancing the welfare of stressed and aggressive cats.

ETHICS

Ethical approval for this study was obtained from the Ethical Review Committee at the Islamic Azad University of Science and Research Branch, Tehran, Iran (Approval Number: IR. IAU. SRB. REC.1400.197), in accordance with the ethical guidelines for animal research. The experiment was supervised by the Iranian Society for the Prevention of Cruelty to Animals, underscoring a commitment to humane treatment.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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