Daily gabapentin improved behavior modification progress and decreased stress in shelter cats from hoarding environments in a double-blind randomized placebo-controlled clinical trial

Bailey H. Eagan

Introduction

Cats housed in shelters commonly experience unmitigated fear, anxiety, and stress.[1,2] Minimizing negative affective states is critical to cat health and welfare in the shelter environment.[3] This is especially important in fearful or undersocialized cats particularly at risk for poor outcomes in shelters,[4,5] such as cats coming from a hoarding environment (HE).[6,7]

HE cats commonly have a high prevalence of medical and behavioral issues,[7–10] with highly varied reported in-shelter survival rates ranging from 0% to 100%.[6,7,11] Despite recognized challenges associated with the successful management of HE cats, recent research found that with investment of staff resources, HE cats may have a length of stay and percentage of animals leaving the shelter alive (or live release rate) comparable to nonhoarded cats.[11] HE cats can also show social behavior in a shelter and adoptive homes.[12] While research increasingly demonstrates that HE cats can be treatable in the shelter, no research has investigated the efficacy of the various treatment options for HE cats, and there are currently no widespread recommended best practices for informing their in-shelter treatment.

Behavioral strategies, such as behavior modification (BMOD) programs, that aim to decrease fear in animals may be beneficial for HE cats. BMOD protocols vary but commonly include respondent and operant conditioning processes and training methods of desensitization, counterconditioning, and positive reinforcement training.[13,14] Counterconditioning methods have resulted in a decrease in some fear-related behaviors in humans and animals.[15,16] Whereas limited information exists on the efficacy and welfare impacts of BMOD methods in shelter cats, BMOD use has been suggested generally in the treatment of fearful shelter cats.[11,14] In an observational study on shelter dogs by Collins et al,[17] the use of a BMOD program resulted in improved behavior in standardized behavior evaluations, BMOD graduation, adoption, and high adopter satisfaction.

Anxiety medications are widely recommended in conjunction with BMOD programs for integrative

treatment plans for fearful animals.[18] A limited body of research demonstrates that anxiety-reducing medication may improve BMOD progression in dogs[19] and cats[20]; however, these studies lack a placebo control, and a caregiver effect of the treatment administrator believing the treatment improved the animal's condition is possible. In shelters, Abrams et al[21] investigated the impact of trazodone given to dogs on shelter intake, compared to historical controls not given trazodone, and found that dogs in the trazodone group showed lower rates of infectious respiratory disease complex, shorter average length of stay, and higher adoptions. To the best of the authors' knowledge, no previous studies have assessed the use of BMOD in the treatment of fearful cats in shelters or the impact of anxiety-reducing medication on cat BMOD progress in shelters.

One medication that may help fearful cats in shelters is gabapentin, a medication used for epilepsy and pain in cats[22,23] and that has also been shown to reduce signs of stress in cats.[24–26] A single dose of gabapentin in cats has resulted in a decreased cat stress score (CSS)[25–27] and improved compliance[25,28–31] during vet appointments compared to a placebo (dose range, 13.0 to 36.0 mg/kg). During a trap-neuter-return program of cats, gabapentin (9.2 to 47.6 mg/kg) resulted in lower CSS compared to placebo and no difference in respiratory rate, global sedation score, or facial injuries.[24] Gabapentin, when prescribed for anxiety, is usually prescribed as a pre-event, fast-acting medication used in advance of stressful events such as veterinary appointments,[18] but no known research has assessed its ongoing use as a daily medication for reducing signs of stress.

This study aimed to assess the impact of daily gabapentin (10 mg/kg) on HE shelter cat BMOD progression, CSS, latency to emerge (LTE) from hiding (a modified emergence test[32]), general in-shelter behavior, day 1 urine suppression,[1] and social scores in post-adoptive homes.[12,33] In addition to assessing behavior and welfare impacts, this study aimed to monitor cat health and the occurrence of possible adverse effects associated with daily gabapentin administration within a shelter setting. We hypothesized that daily gabapentin would predict faster BMOD progression, lower CSS, LTE, urine suppression, and stress-related behaviors and may result in higher post-adoptive social scores compared to cats receiving a placebo while in the shelter. Based on previous safety data, we did not anticipate adverse outcomes of long-term gabapentin administration.

Methods

Ethics approval

This study was approved by the University of British Columbia's Animal Care Committee (A21-0088) and Behavioral Research Ethics Board (H22-00418) and the British Columbia Society for the Prevention of Cruelty to Animals (BC SPCA) Research Committee. All methods and results are

reported in accordance with the Animal Research: Reporting of In Vivo Experiments guidelines[34] and Consolidated Standards of Reporting Trials guidelines[35] where applicable.

Study site, animals, and daily care

This study was conducted at the BC SPCA Richmond Branch (Richmond, BC, Canada) from June to December 2021. All research and care activities were conducted 7 d/wk between 8:00 and 20:00. The shelter had restricted public access throughout the project as the site was used solely to treat cats entering the shelter from HEs.

No formal power calculations were conducted, rather a desired sample size was determined on the basis of sample sizes of comparable studies.[24–26] Upon intake, cats (n = 37) entered the shelter facility in staggered intakes from 3 cat hoarding cases (cases A through C). On intake, health condition was assessed and approximate age groups were assigned accordingly, as follows: kitten (under 6 months), young adult (7 months to 3 years), adult (4 to 7 years), and senior (8 years or older). The study inclusion criteria required that a cat was deemed to have moderate or severe fear (herein called "fearful cats") by a veterinary behaviorist (KVH). Fearful classification was determined by a combination of case history (fearful behavior of cats in response to animal protection officers in the field), levels of escape, freezing, and other panicked behavior during the intake examination and in-cage behavior when in the shelter (showing a lack of prosocial behavior toward people, consistently hiding, or not showing signs of normal exploratory behavior within 12 to 24 hours after intake). Study intake criteria also required that cats not have systemic disease states that would significantly affect behavior or ability to metabolize medications and not show signs of pregnancy. Cats that were not eligible for the study received care as per standard shelter protocols. Of 37 cats, 32 met the study criteria. Cats that did not meet study criteria included 2 that had grade 6/6 heart murmurs and cardiomegaly on radiography, 2 that did not show moderate to severe fear during intake, and 1 cat that was visibly pregnant.

Only cats from within a single hoarding case were in the shelter at a given time, and the shelter's maximum physical holding capacity for cats was 12. Upon intake, the cats were singly housed in double-compartment portalized enclosures (1.5 X 0.7 X 0.6 m), separated between 3 rooms by sex (the third room was used for isolation or special care cases as needed; eg, pregnant cats). Each enclosure consisted of a hidebox (Hide, Perch & Go box; BC SPCA), a litter box with clumping litter (Arm & Hammer Double Duty Clumping Litter; Church & Dwight Co Inc), food, water, a bed, and a toy (soft toy, ball, and/or circular roller toy). Staff occasionally draped a pillowcase over the front of 1 section of the enclosure to provide additional concealment opportunities for cats within the enclosure beyond the hidebox. Each room included open floor space that allowed for group housing once a cat reached a treatment benchmark of consistently eating, drinking, and using the litter box. The daily

shelter routine included feeding, cleaning, and the research protocols described below. Occasionally, shelter care required additional procedures (eg, vaccines and baths), of which the date and time were noted. Ongoing monitoring for health concerns or medication side effects was conducted daily. Twice daily, at approximately 8:30 and 19:30, shelter staff conducted daily welfare assessments, including recording for signs of eating, drinking, and using the litter box, and observed for any clinical signs of diarrhea, vomiting, lethargy, sedation, and ataxia. If any other abnormal observations were noted throughout the day by research staff, they were recorded on the daily welfare assessment forms.

Video monitoring

Cats were video monitored using indoor cameras (Nest camera; Google) placed inside cat cages. Additional cameras were placed facing cage banks, approximately 2 m away. All Nest cameras recorded continuously 24/7 for each cat, from their intake in the shelter until their outcome. For behavioral video coding, video clips were manually extracted into 1-minute time-lapse clips (containing 12 hours of continuous video recording in time-lapse form), and video clips were stored locally and on Microsoft OneDrive.

Gabapentin or placebo assignment and administration

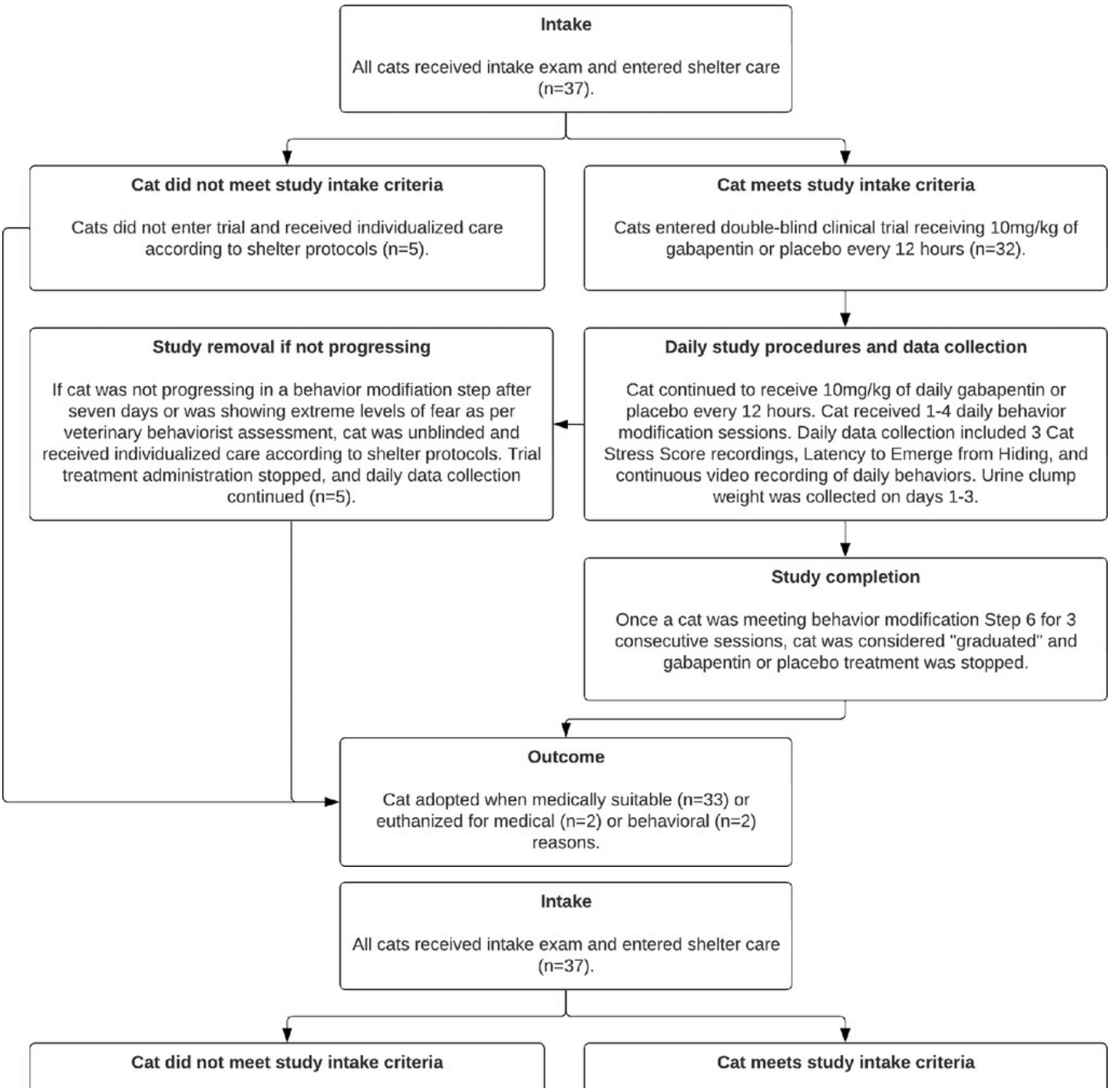
All eligible fearful cats (n = 32) entered into 1 of 2 parallel treatment groups: gabapentin and daily BMOD (17) or placebo and daily BMOD (15). Gabapentin and placebo oral suspensions (100 mg/mL fish-flavored oil) were prepared from bulk substances at a compounding pharmacy (MacDonald's Prescriptions and Medical Supplies). Stevioside, 95% powder (0.2 g/100 ml), fish-flavored oil (3 ml/100 ml), and a fixed oil suspension vehicle (qs 100 ml; PCCA) were used for both preparations to ensure treatments were indistinguishable from one another. For the gabapentin suspension only, 10 g/100 ml of gabapentin was added **(**Supplementary Figure S1**)**. Care was taken to ensure that preparations looked identical and were not possible to distinguish by staff or the research team.

On intake, cats were randomly assigned to the gabapentin or placebo treatment group using a 3-step blinding protocol **(**Supplementary Appendix S1**)**. Treatment keys were confidentially maintained by a 2-person veterinary team external to the research project. The research team and shelter staff remained blinded to each cat's treatment until project completion, unless unblinding was required for welfare reasons based on predetermined criteria indicating lack of progression or extreme fear **(**Supplementary Figure S2**)**.

Cats in both treatment groups received 10 mg/kg of a liquid suspension of gabapentin or placebo approximately every 12 hours (at 8:00 and 19:30). To administer each treatment, progressive attempts included offering the treatment in small servings of high-value wet food; second, placed on front paws with a syringe (and with confirmation of ingestion through the cat licking the suspension);

or third, orally through a Tom Cat catheter (Tyco Healthcare)[24] or syringe if neither of the earlier options were successful. If none of these administration methods were successful without the cat actively trying to escape, the treatment was considered missed and recorded as so. After each medication administration, the research team recorded the approximate percentage of medication successfully ingested by each cat and the method of administration (food, mouth, or paws).

The shelter pathways for study cats are summarized **(**Figure 1**)**, and each procedure is described in further detail below. Study participants received 1 to 4 daily BMOD sessions. Daily data collection included 3 CSS recordings, LTE from hiding, and continuous video recording for behavioral ethogram recordings. Further, on days 0 to 4 in the shelter, urine clump weights were collected.



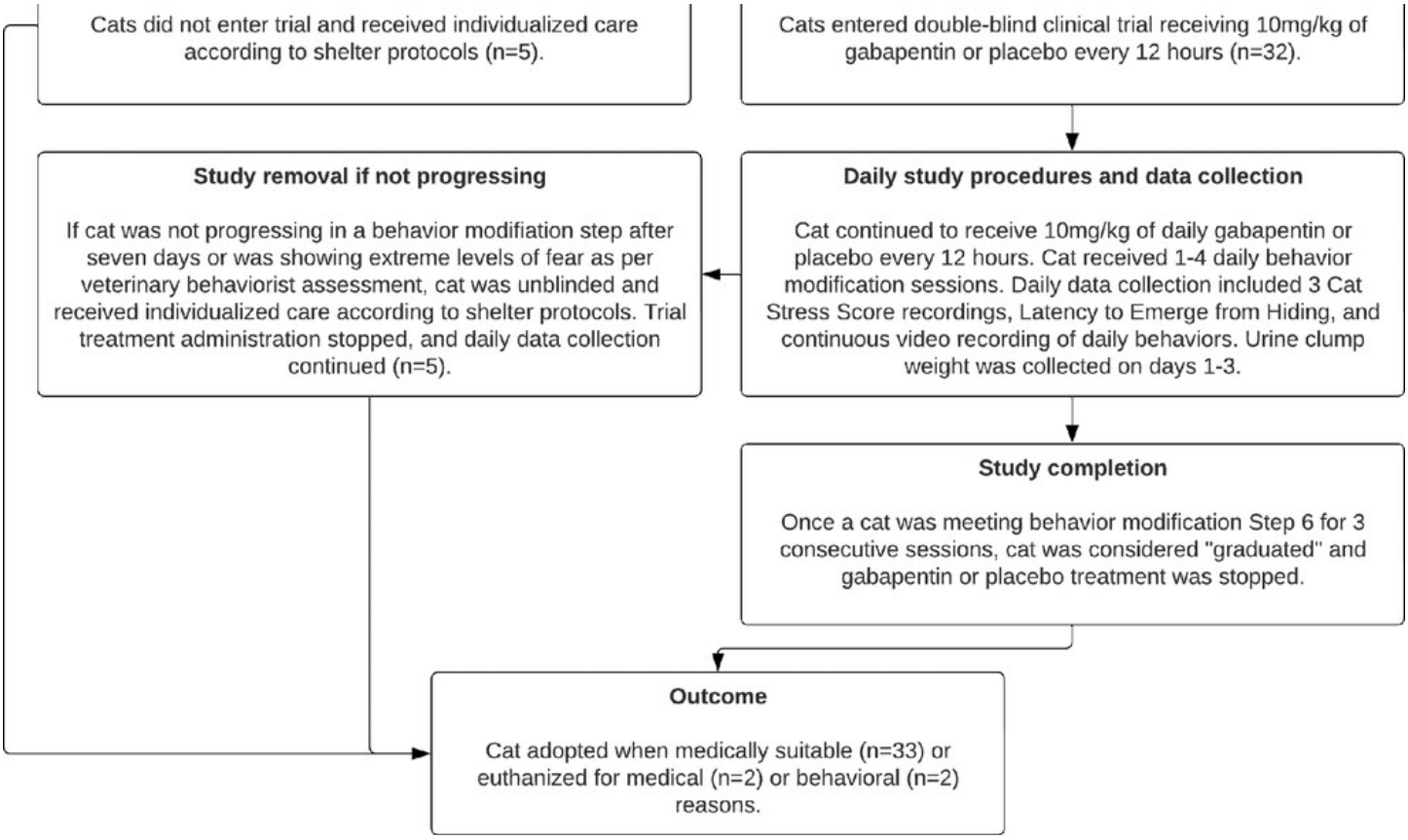


Figure 1

Flow diagram for a double-blind randomized placebo-controlled clinical trial to evaluate the impact of gabapentin (10 mg/kg, PO, q 12 h) on behavior modification (BMOD) progression and signs of stress in fearful shelter cats (n = 37) from 3 hoarding environments (case A, B, or C) between June 18, 2021, and December 10, 2021.

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Behavior modification

A daily standardized BMOD program was used for all fearful cats in this study **(**Figure 2**)**.[36] Overall, the goal of the BMOD program was to use counterconditioning (repeatedly pair the sight of a human with food) and systematic desensitization (incremental steps of difficulty), aiming to decrease fear of humans and increase the desire for human social contact. BMOD sessions were completed twice daily at approximately 10:00 and 16:00. However, rare occurrences of a varied number of BMOD sessions on specific days occurred (range, 1 to 4 sessions daily). A mean daily BMOD score was calculated, and if a cat was not progressing to the next step in the BMOD program after 7 days, the cat was unblinded and received individualized care. To assess the strength of inter-rater reliability between observers for BMOD score assignment, a secondary observer joined 19 (2.0%) BMOD sessions. Both the research staff conducting BMOD and the secondary observer independently assigned a BMOD score. To assess inter-rater agreement for BMOD, intraclass correlation coefficients (ICCs)[37,38] were computed between the primary researcher's BMOD and the secondary observer's independently recorded scores.

Increase both the duration and intensity of petting if the cat shows signs of tolerating this well. Continue petting for short periods after treats are finished to test if the cat has learned to enjoy petting.

the hand is removed. As the cat becomes more comfortable, incorporate gentle movements of the first hand or touch stick, then start incorporating light touch (barely grazing the top of the fur) behind the ears or on the back of the neck.

Behavior Modification Tips and Tricks

- Go slow and steady - patience is key!
- Use a quiet voice, slow movements, and avoid looking a fearful cat directly in the eyes.
- To begin, keep each session brief (approximately 2-3 minutes).
- Try a wide variety of high-value treats to determine a cat's preference (e.g. wet food or treats, canned fish, squeeze-up treats, dry or moist food or treats)
- Watch body language carefully to ensure the cat is comfortable. **Do not force interaction**. If the cat is highly fearful or showing aggression, go back to an earlier step without contact, or stop the session.
- Anxiety-reducing medication may be beneficial in a cat's behavior modification program progression. Discuss options with your veterinarian.

Step 6: Seeking Attention Without Food

Observe if the cat will seek human attention without treats. When interacting, positive signs may include a cat leaning into pets, purring, and/or kneading with its feet. When petting stops, they may move toward the hand, lick or paw at the hands to solicit pets. When the cat is voluntarily approaching most people seeking physical contact, they are ready to graduate from the behavior modification plan!

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V1 Guide by Bailey Eagan.
Dr Karen van Haaften & Dr Alexandra Protopopova.
Cat Illustrations by Luck Dannan.

Behavior Modification for Fearful Cats

Step 1: Meeting Minimum Welfare Criteria

Before beginning a behavior modification plan, make sure the cat it is eating, drinking, and using the litter box, at least when people are not around. This is to ensure we do not inappropriately add stress to the cat. Once the cat is meeting these criteria, begin behavior modification using the following steps.

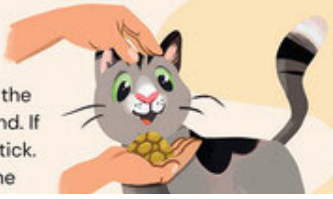
Step 2: Eating with Person in Room

Offer the cat high-value food in a bowl while a person sits quietly in the same room approximately 3 feet away.

Step 3: Eating From Hands

First, offer the cat food using an extension of a hand such as a long spoon or touch stick. As the cat becomes comfortable eating from the hand extender, gradually move the hand up the handle toward the cat, until they are eating from the person's hand.

Step 4: Allowing Light Touch



Slowly and gently reach an empty hand toward the cat followed by offering food from the other hand. If using the hand feels unsafe, switch to a touch stick. Retract food hand and petting hand at the

Step 5: Increasing Petting and Scratching

Figure 2

Infographic depiction of the standardized BMOD program used in the study described in Figure 1. All eligible study cats (n = 32) received BMOD, regardless of their assigned treatment group. Image reproduced with permission by Bailey H. Eagan, Dr. Karen van Haaften, and Dr. Alexandra Protopopova, the copyright holders; all rights reserved. Individuals wishing to reproduce the image should contact Bailey H. Eagan at bailey.eagan@ubc.ca.

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Cat stress score

The CSS, a qualitative behavioral assessment ranging from 1 (fully relaxed) to 7 (terrified),[27] was recorded 3 times daily in person (at approx 8:00, 1:00, and 18:00). To determine the CSS, an observer stood approximately 1 m from the target cat, observed the cat for 60 seconds, and then assigned a category (score) based on the description of the behaviors. To assess the inter-rater reliability between observers, a secondary observer independently scored 49 (4.1%) CSS video recordings in addition to the primary researcher. To assess inter-rater agreement for CSS, ICC[37,38] was computed between the primary researcher's CSS and the secondary observer's independently recorded scores.

LTE from hiding

LTE is commonly used to measure fear or boldness in animals.[32,39] LTE from hiding after staff left the shelter was recorded daily using in-cage Nest cameras. LTE was recorded from when the last person left the room at the end of the day to when each cat emerged from their enclosure hidebox. Cats were scored as they emerged from hiding if > 50% of their bodies were outside the hidebox. If a cat was outside the hidebox when the last person left the room, the LTE was scored as 0 minutes. A secondary observer independently scored 9 (1.6%) LTE sessions from stored video to assess the strength of inter-rater reliability between observers for LTE. To assess inter-rater agreement for LTE, ICC[37,38] was computed between the primary researcher's LTE and the secondary observer's independently recorded scores.

Urine suppression

Urine clump weight was collected on days 1, 2, and 3. To ensure consistent access to water, on days 0 to 4, 500 mL of water was measured and given to cats in a water bowl in their cage in the evening. Other days, water was not measured. To measure urine clump weight for urine suppression calculations, before litter boxes were cleaned in the morning, a paper weigh boat was placed on a digital kitchen scale and tared to 0. The urine clump was collected using a slotted plastic litter scoop, and the clump weight recorded. To quantify urine suppression from urine clump weights, a urine suppression value was calculated for each cat using the below formula from Andrukonis et al.[1] Urine suppression has been found to correlate with stress-related behavior in cats in shelters.[1]

$$\frac{\text{Average (days 2 and 3 clump weights)} - \text{day 1 clump weight}}{\text{Average (days 2 and 3 clump weights)}}$$

$$\frac{\text{Average (days 2 and 3 clump weights)} - \text{day 1 clump weight}}{\text{Average (days 2 and 3 clump weights)}}$$

Ethogram behaviors

To monitor daily in-shelter behavior, a behavioral ethogram adapted from Stella[40] consisting of maintenance, social, and exploratory behaviors, was scored using continuous time-lapse videos. One-zero sampling[41] was used to manually record the presence or absence of a particular behavior within a 5-second sample interval of time-lapse video (equal to 1 hour of real-time recording). To assess inter-rater reliability between observers for behavioral ethogram scoring, a secondary observer independently scored 60 hours (1.1%) of stored videos.

Post-adoption surveys

To assess social behavior in homes, post-adoption surveys were conducted at 1 month and 1 year post-adoption. Adopters were given a condensed Feline Behavioral Assessment and Research Questionnaire survey[33] for which Likert-scale questions were used, and responses were scored numerically as follows: always (5), often (4), sometimes (3), rarely (2), or never (1). Open-ended questions relating to socialization status were scored as follows: supersocial (4), social (3), undersocial (2), and unsocial (1) based on the socialization scoring system of Jacobson et al[12] **(**Supplementary Appendix S2**)**.

Statistical analysis

All statistical analyses were conducted in RStudio (version 2022.02.3 “Prairie Trillium” release for macOS; Posit Software PBC).[42] All data were analyzed on an intention-to-treat (ITT) and per-protocol (PP) basis.[43] Under ITT analysis, which was conducted to assess the effect of assigning cats to treatments, data were analyzed on the basis of the treatment group (gabapentin or placebo) to which the cats were initially assigned. However, not all cats could receive their originally intended gabapentin or placebo doses due to resisting medication administration or being removed from the study. Therefore, PP analysis, which was conducted to assess the effect of receiving treatment, was also conducted, analyzing differences in treatment groups of cats that received over 75% of their intended doses.

Descriptive statistics were calculated for days to graduate from the BMOD program overall and for each treatment group. For CSS, LTE, and ethogram behaviors, outcomes were converted into binary classes.

Time-to-event analyses comparing time to graduate in days and time to each BMOD step between treatment groups were performed using the Kaplan-Meier product limit method and log-rank test to assess whether there were statistically significant differences between treatment groups.[44] Cats were considered censored (indicating missing information regarding their time to event) on the event day if

they were transferred before BMOD graduation (n = 2) or unblinded (5). Hazard ratios (HRs) were calculated to estimate the risk of BMOD graduation between treatment groups at a given time point, and a Cox proportional hazard model was then used to evaluate the effect of treatment on time to graduation after adjusting for the potential confounders of hoarding cases and sex.

A mean daily CSS was calculated for all cats. To model CSS and LTE, outcome variables were converted into binary classes (coded as 0 or 1), indicating low and high values, respectively. The cutoff for assigning an observation to the 1 or 0 class was based on the 50th percentile for CSS and 75th percentile for LTE (to allow for a more clinically relevant cutoff value of 77 minutes, compared to the 50th percentile of 11 minutes). Mixed-effects modeling was conducted using the *glmer* function in the *lme4 R* package (The R Project for Statistical Computing) with independent variables including treatment (gabapentin or placebo), case, and sex. Cat-ID was included as a random effect.

Daily proportions and counts of each behavior were calculated for each study cat and visually explored for trends over time or apparent differences between treatment groups. Behavior proportions were converted into binary classes (coded as 0 or 1), indicating low and high values. The cutoff for assigning an observation to the 1 versus 0 class was based on the 50th percentile. Mixed-effects modeling was conducted with independent variables, including treatment (gabapentin or placebo), case, and sex. Cat-ID was included as a random effect.

To assess the impact of gabapentin on urine suppression, a Wilcoxon signed rank test[45] was conducted, comparing urine suppression values between the gabapentin and placebo groups. For PP analysis assessing the effect of receiving treatment on urine suppression, cats were included in the analysis if they received over 75% of their intended doses on days 1 to 3 only.

Due to limited respondents to post-adoption surveys (n = 7; 22% response rate), results were explored descriptively.

Results

Across 3 separate intakes of cats coming from HEs, 32 of 37 (86.4%) were enrolled in the clinical trial due to having substantial fear. Of these cats, 28 of 32 (87.5%) graduated from the BMOD program regardless of the treatment group and were subsequently adopted. Two cats were transferred at BMOD stage 5 due to insufficient shelter capacity and ultimately adopted, and 2 were euthanized for behavior issues (ongoing severe fear of people). The median time to graduate from the BMOD program was 11 days (range, 4 to 51 days). All 32 fearful cats entered into the trial were included in the ITT analysis, and 27 of 32 cats that received over 75% of their overall intended doses were included in the PP analysis **(**Table 1**)**. No adverse side effects were noted due to treatment administration. Diarrhea was noted intermittently in all cats in case A and persisted after gabapentin or placebo was stopped.

Table 1

Demographic characteristics of 37 fearful healthy cats moved from 3 hoarding environments (case A, B, or C) to a shelter facility and enrolled in a double-blind randomized placebo-controlled clinical trial to evaluate the impact of gabapentin (10 mg/kg, PO, q 12 h) on behavior modification progression and signs of stress in fearful shelter cats between June 18, 2021, and December 10, 2021, stratified by inclusion in analyses (intention-to-treat [ITT] analysis and per-protocol [PP] analysis) and by treatment group (gabapentin or placebo).

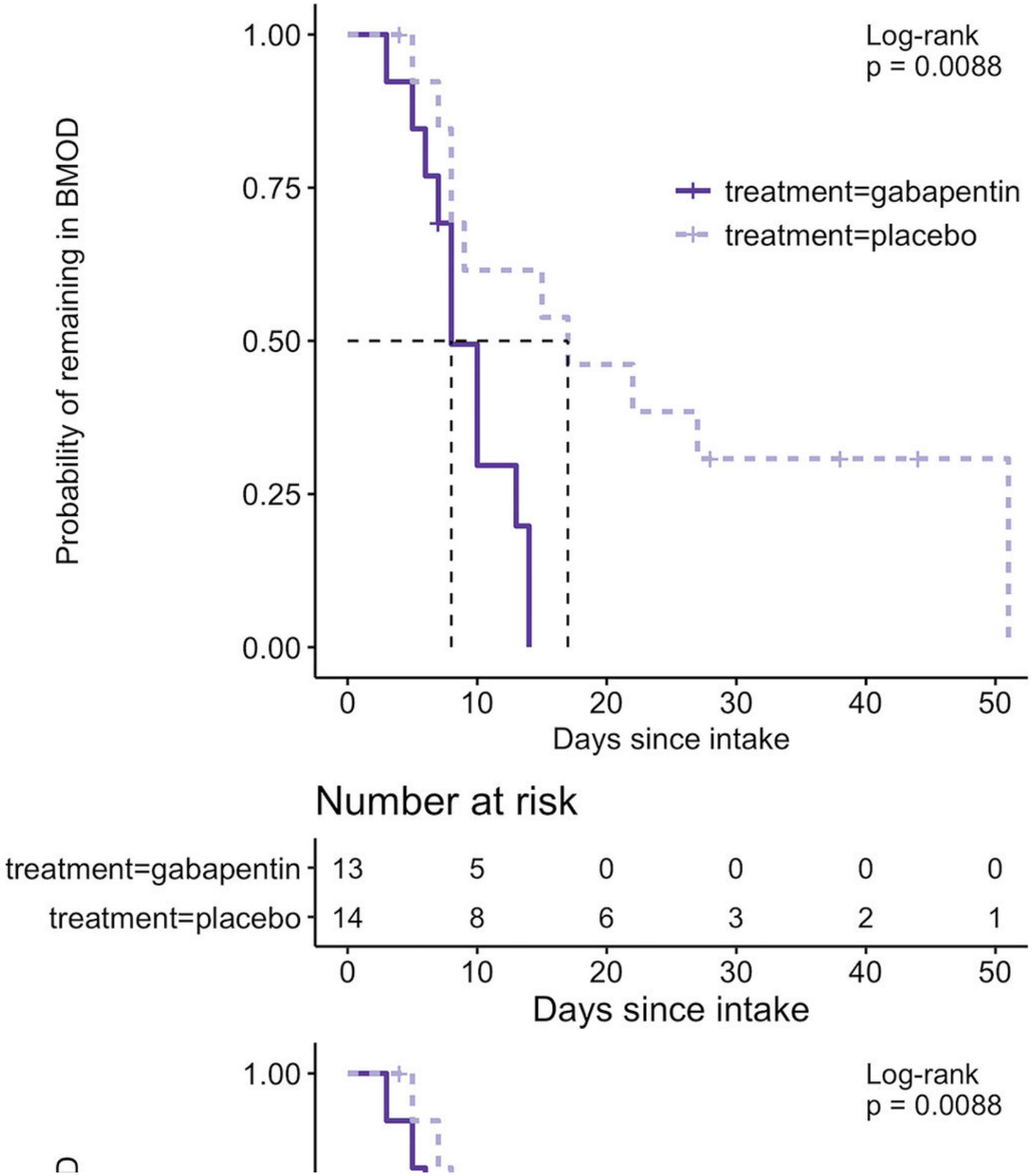
Variable	ITT gabapentin, n = 17 (53.1%)	ITT placebo, n = 15 (46.8%)	PP gabapentin, n = 13 (48.1%)	PP placebo, n = 14 (51.8%)
Age group				
Kitten	2 (6.2%)	1 (3.1%)	1 (3.7%)	1 (3.7%)
Young adult	7 (21.8%)	7 (21.8%)	4 (14.8%)	6 (22.2%)
Adult	5 (15.6%)	4 (12.5%)	5 (18.5%)	4 (14.8%)
Senior	3 (9.3%)	3 (9.3%)	3 (11.1%)	3 (11.1%)
Sex				
Female	11 (32.3%)	10 (31.2%)	9 (33.3%)	9 (33.3%)
Male	6 (18.7%)	5 (15.6%)	4 (14.8%)	5 (18.5%)
Case				
A	3 (9.3%)	1 (9.3%)	2 (7.4%)	1 (3.7%)
B	11 (34.3%)	11 (34.3%)	10 (37.0%)	11 (40.7%)
C	3 (9.3%)	3 (9.3%)	1 (3.7%)	2 (7.4%)

Data are presented as numbers and percentages.

Medication was administered through food, on paws and licked off, or by mouth (through a syringe or catheter and syringe). The mean estimated percentage of ingested dose (gabapentin or placebo) was 85% for administration in food (n = 431 doses), 50% for placement of doses on front paws (69 doses), and 97% for syringe feeding by mouth (489 doses).

The distributions of outcome variables were visualized using histograms, and in each case, the distribution was nonnormal. Time to graduate PP analysis showed a statistically significant difference by log-rank test, with cats in the gabapentin group graduating the BMOD program faster than cats in the placebo group (P = .008; Figure 3). PP analysis of time to steps 4, 5, and 6 showed a statistically significant difference by log-rank test, with cats in the gabapentin group reaching each step faster than cats in the placebo group (P = .018, P = .012, and P = .044, respectively). No statistically

significant differences were observed in PP analysis between days to step 1, 2, or 3 (P = .168, P = .377, P = .329, respectively; Supplementary Figure S3). ITT analysis showed no statistically significant differences between the treatment group for time to graduate or time to steps 1 to 6 (graduate, P = .440; step 1, P = .300; step 2, P = .363; step 3, P = .159; step 4, P = .184; step 5, P = .108; and step 6, P = .678).



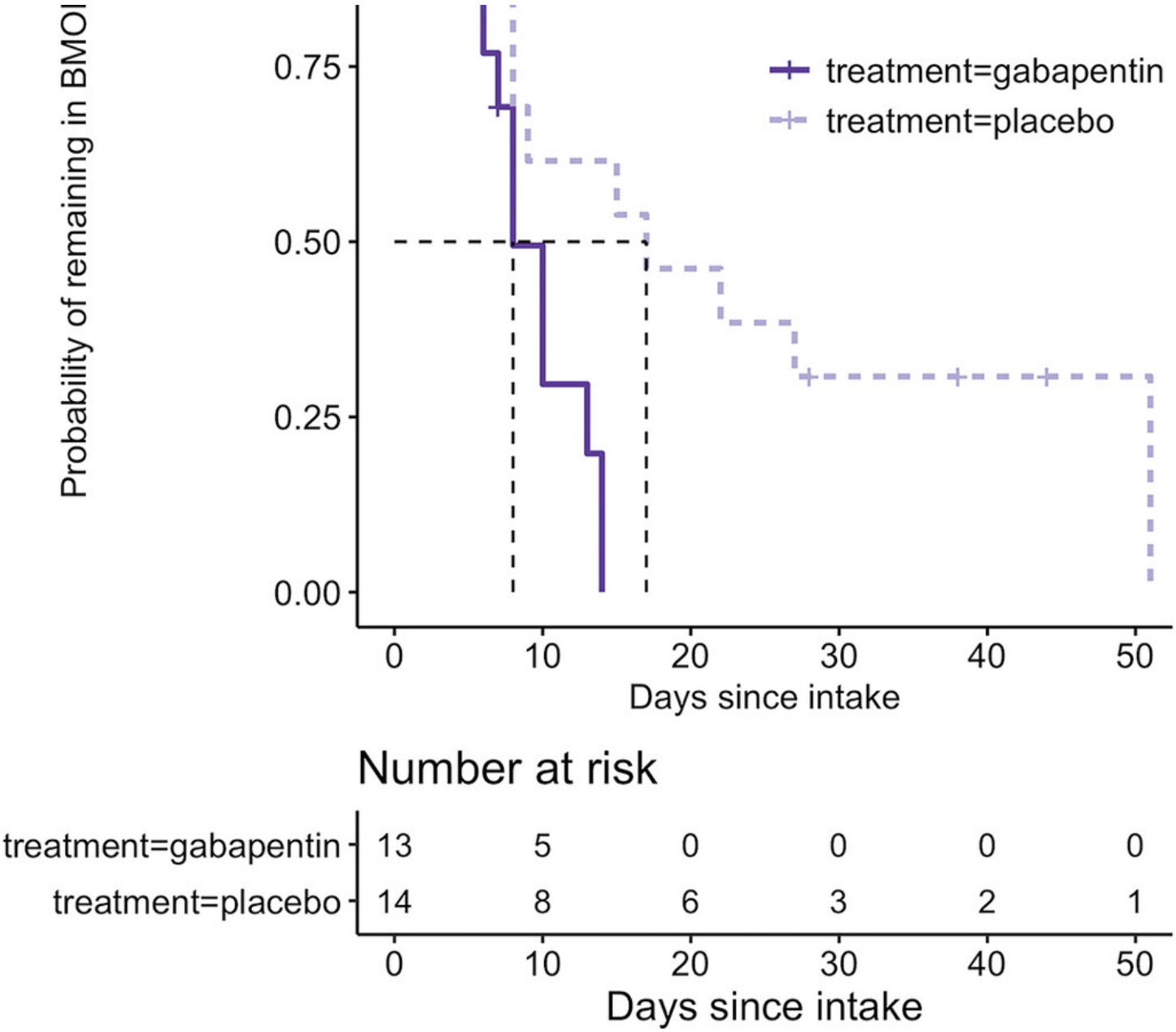


Figure 3

Kaplan-Meier curve visualizing the probability of remaining in the BMOD program (not graduating) over days between gabapentin and placebo treatment groups for the cats described in Figure 1. The per-protocol log-rank test (analyzing 27 cats that received > 75% of their doses) showed a statistically significant difference between treatment groups (P = .008). The value of LD^{50} represented by the dotted black line shows the days for half the population within each treatment group to graduate (LD^{50} for gabapentin = 9 days and LD^{50} for placebo = 18 days).

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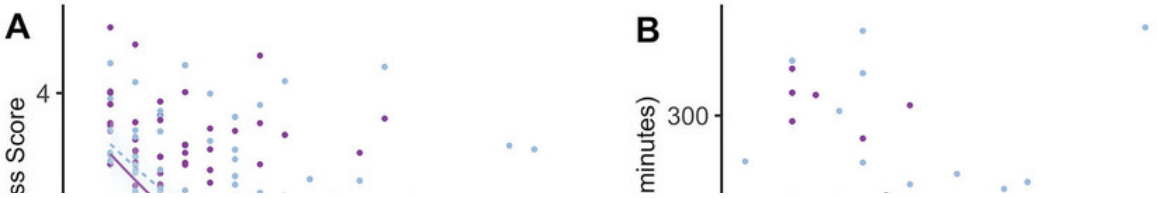
Cox proportional hazard PP analysis showed that gabapentin had a higher HR of graduating the BMOD program compared to placebo (HR = 4.03; 95% CI, 1.31 to 12.4; P = .015). No statistically significant differences were observed in the HR of graduating between cases (case B HR = 1.98; 95% CI, 0.25 to 15.6; P = .518; case C HR = 0.71; 95% CI, 0.062 to 8.2; P = .780, compared to case A), or in males compared to females (HR = 0.67; 95% CI, 0.261 to 1.7; P = .420; Supplementary Figure S4). Cox proportional hazard ITT analysis showed no statistically significant differences in gabapentin compared to placebo (HR = 1.91; 95% CI, 0.79 to 4.6; P = .152), case A compared to case B (HR = 5.27; 95% CI, 0.64 to 43.6; P = .124), or case C (HR = 1.65; 95% CI, 0.18 to 15.6; P = .660). No statistically significant difference was observed in the HR of graduating from the BMOD program in males compared to females (HR = 0.67; 95% CI, 0.261 to 1.7; P = .415).

PP analysis of CSS showed a statistically significant relationship of decreasing over time (OR = 0.79; 95% CI, 0.75 to 0.83; P < .001), gabapentin showed lower CSS than placebo (OR = 0.24; 95% CI, 0.07 to 0.79; P = .019), and case C showed higher CSS than case A (OR = 11.0; 95% CI, 1.59 to 75.9; P = .015; Figure 4). No statistically significant difference was observed in the PP analysis of CSS in case B compared to case A (OR = 2.93; 95% CI, 0.09 to 7.07; P = .840) or in males compared to females (OR = 2.93; 95% CI, 0.84 to 10.2; P = .092). ITT analysis of CSS showed a statistically significant relationship of decreasing over time (OR = 0.79; 95% CI, 0.75 to 0.82; P < .001), and gabapentin showed lower CSS compared to placebo (OR = 0.24; 95% CI, 0.06 to 0.94; P = .041). ITT analysis of CSS showed no statistically significant differences between sex (OR = 2.2; 95% CI, 0.53 to 9.18; P = .278), between cases A and B (OR = 4.19; 95% CI, 0.53 to 33.2; P = .174), or between cases A and C (OR = 0.29; 95% CI, 0.03 to 3.26; P = .318).



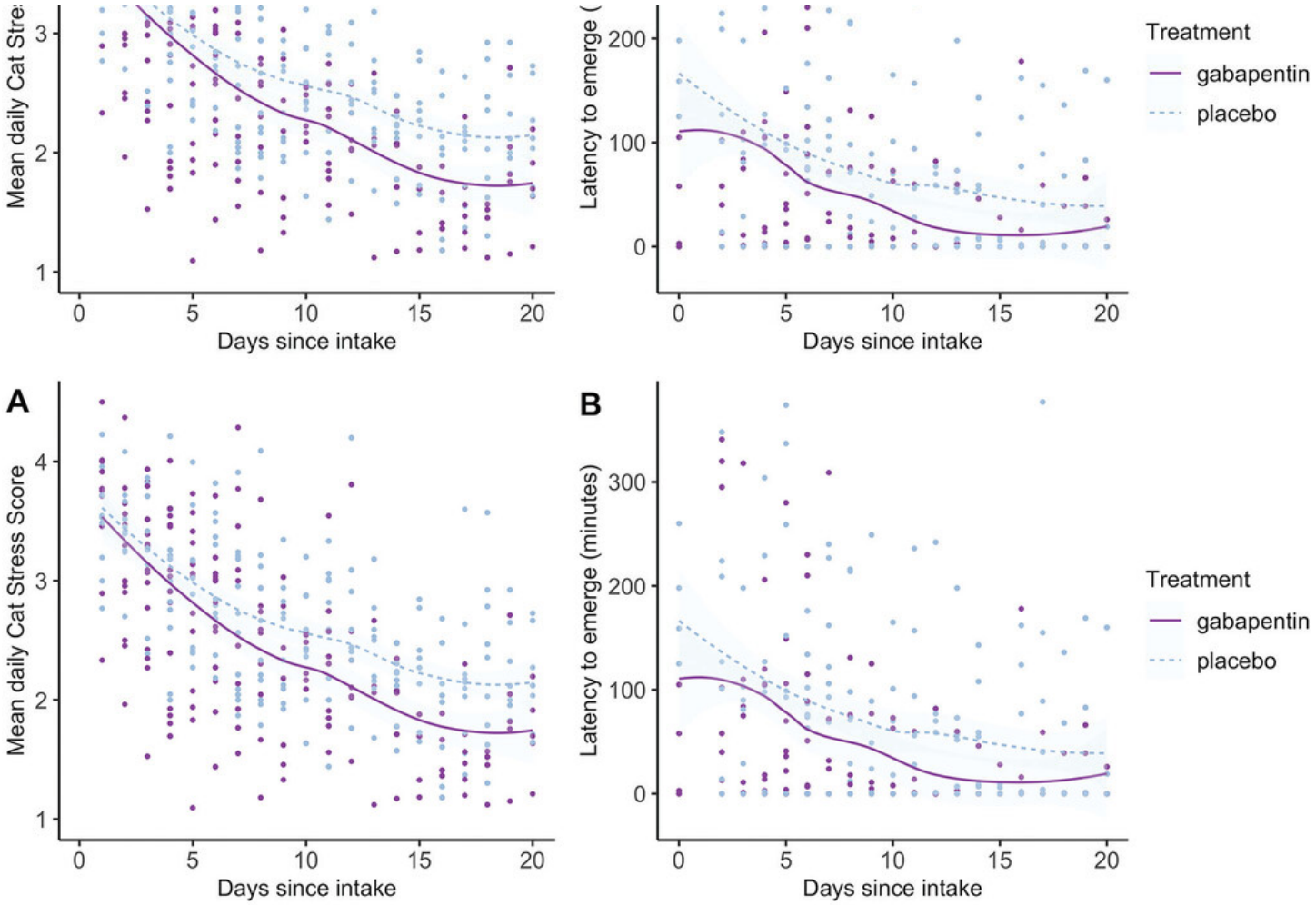


Figure 4

Loess-smoothed mean daily cat stress score (CSS; A) and latency to emerge (LTE; B) for the cats described in Figure 1. The lines depict results for per-protocol (cats that received > 75% of their doses) treatment groups of gabapentin (n = 13) or placebo (14) beginning at intake and ending at day 20. The shaded area on either side of the lines represents the 95% CI. A—The CSS decreased significantly over time (OR = 0.79; 95% CI, 0.75 to 0.83; $P < .001$), and cats in the gabapentin group had lower CSSs than cats in the placebo group (OR = 0.24; 95% CI, 0.07 to 0.79; $P = .01$). B—The LTE decreased significantly over time (OR = 0.88; 95% CI, 0.84 to 0.92; $P < .001$), and cats in the gabapentin group had lower LTE, compared to cats in the placebo group (OR = 0.13; 95% CI, 0.03 to 0.59; $P = .008$).

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Figure 4

Loess-smoothed mean daily cat stress score (CSS; A) and latency to emerge (LTE; B) for the cats described in Figure 1. The lines depict results for per-protocol (cats that received > 75% of their doses) treatment groups of gabapentin (n = 13) or placebo (14) beginning at intake and ending at day 20. The

shaded area on either side of the lines represents the 95% CI. A—The CSS decreased significantly over time (OR = 0.79; 95% CI, 0.75 to 0.83; $P < .001$), and cats in the gabapentin group had lower CSSs than cats in the placebo group (OR = 0.24; 95% CI, 0.07 to 0.79; $P = .01$). B—The LTE decreased significantly over time (OR = 0.88; 95% CI, 0.84 to 0.92; $P < .001$), and cats in the gabapentin group had lower LTE, compared to cats in the placebo group (OR = 0.13; 95% CI, 0.03 to 0.59; $P = .008$).

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PP analysis of LTE showed a statistically significant relationship of decreasing over time (OR = 0.88; 95% CI, 0.84 to 0.92; $P < .001$), gabapentin showed lower LTE compared to placebo (OR = 0.13; 95% CI, 0.03 to 0.59; $P = .008$; Figure 4), and case B showed higher LTE than case A (OR = 157; 95% CI, 5.65 to 4350; $P = .003$). No statistically significant difference was observed between cases A and C (OR = 1.31; 95% CI, 0.03 to 60.9; $P = .890$) or in males compared to females (OR = 2.63; 95% CI, 0.54 to 12.8; $P = .230$). ITT analysis of LTE showed a statistically significant relationship of decreasing over time (OR = 0.86; 95% CI, 0.83 to 0.90; $P < .001$), gabapentin showed lower LTE than placebo (OR = 0.11; 95% CI, 0.02 to 0.50; $P = .004$), and case B showed higher LTE compared to case A (OR = 316; 95% CI, 11.7 to 8,528; $P < .001$). No statistically significant difference was observed in case C compared to case A (OR = 2.11; 95% CI, 0.05 to 92.3; $P = .700$) or in males compared to females (OR = 2.58; 95% CI, 0.52 to 13.0; $P = .250$). There was a high ICC agreement between the 2 observers for BMOD scores (ICC = 0.84; $P < .001$), CSS (ICC = 0.85; $P < .001$), LTE (ICC = 1.0; $P < .001$), and behavioral ethogram scores (ICC = 0.92; $P < .001$).

Daily proportions and counts of each behavior were calculated for each study cat by day, and behaviors with total proportions under 10% were removed. Based on visual trends **(**Supplementary Figure S5**)**, behaviors selected for further analysis were hiding, perching, lying down, sleeping, and standing. For PP and ITT analyses, no statistically significant differences were observed between treatment groups for daily proportions of behaviors hiding, perching, lying down, sleeping, or standing. For PP analysis, sleeping behavior increased over days (OR = 1.06; 95% CI, 1.02 to 1.10; $P = .006$). Case C showed more hiding behavior (OR = 0.23; 95% CI, 0.06 to 0.86; $P = .029$) and more perching behavior than case A (OR = 9.53; 95% CI, 1.51 to 60.2; $P = .017$). Perching behavior (OR = 1.08; 95% CI, 1.04 to 1.12; $P = .001$) and sleeping behavior (OR = 1.05; 95% CI, 1.02 to 1.08; $P = .003$) increased over days. Case C showed more perch behavior than case A (OR = 7.76; 95% CI, 1.07 to 56.4; $P = .043$). For ITT analysis, hiding behavior (OR = 0.96; 95% CI, 0.93 to 0.99; $P = .005$) and lying down behavior (OR = 0.86; 95% CI, 0.93 to 0.99; $P = .020$) decreased over days.

In the PP analysis, the median urine suppression for cats in the placebo group (n = 10) was 0.42 (range, 0 to 1) and the median in the gabapentin group (13) was 0.23 (range, −2.16 to 0.77). The

Wilcoxon test showed that the difference for PP analysis was statistically significant (P = .027, effect size r = 0.54). For ITT analysis of urine suppression, the median urine suppression for cats in the placebo group (n = 10) was 0.42 (range, 0 to 1) and the median urine suppression for cats in the gabapentin group (7) was 0.22 (range, −2.16 to 0.77). The Wilcoxon test showed that the difference for ITT analysis was not statistically significant (P = .075, effect size r = 0.37).

Due to limited respondents (n = 7), results were explored descriptively only for post-adoption surveys and comparisons between treatment groups could not be made. During the first week post-adoption, cats were scored as undersocial (1.4 ± 0.5), but 1 year post-adoption, adopters reported higher social or supersocial scores (3.4 ± 0.5). One year post-adoption, cats were commonly reported to be comfortable being petted by or when playing with a familiar (household) persons (mean ± SD, 4.5 ± 0.5) but seldom comfortable being petted by or when playing with unfamiliar (nonhousehold) persons (2.3 ± 0.8) and seldom comfortable and relaxed among people during social gatherings (2.2 ± 0.5).

Discussion

The results of this study showed that daily gabapentin given at 10 mg/kg every 12 hours was beneficial in the behavioral treatment of cats from HEs, as evidenced by faster progression through the BMOD program, a decreased behavioral CSS, a reduced LTE from hiding when staff left for the night, and less urine suppression compared to the placebo group. Notably, the median time to graduation was reduced by half with the administration of gabapentin, with the benefits occurring for later steps of the BMOD program. Additionally, this study generally found a high BMOD program completion and adoption rate, 28 of 32 (87.5%), regardless of the treatment group. This supports growing evidence that cats from HEs can be highly treatable in shelters.[11,12] These results are consistent with the hypothesis that daily gabapentin would predict faster BMOD progression and lower CSS, LTE, and urine suppression.

Among limited survey respondents (n = 7), despite showing unsocial behavior in the first week at home and among unfamiliar people, cats from HEs were reported to show social or supersocial behavior 1 year post-adoption, supporting that cats from HEs can be social companion animals in homes postadoption.[12] Due to limited respondents, we were unable to assess differences in post-adoption behavior between treatment groups.

The 10 mg/kg every 12 hours dose of gabapentin used in this study is a low dose relative to other reported ranges.[24–26] While some previous studies have reported side effects, including sedation,[26,29] ataxia,[25,29] hypersalivation,[24,25] and vomiting,[25,26,28] as hypothesized, no adverse side effects were noted in the present study. Further, no statistically significant differences were observed between gabapentin or placebo groups in behaviors potentially indicative of levels of sedation, including hiding, perching, lying down, sleeping, or standing. However, our behavioral ethogram

recording method included some limitations that are discussed below. Overall, despite a lack of dose-determination studies for the anxiety-reducing effects of gabapentin in cats, this study supported the efficacy and safety of 10 mg/kg every 12 hours of gabapentin for the in-shelter treatment of healthy fearful cats. This reflects the reported recommended dose of 3 to 10 mg/kg for cats for situational fear and anxiety noted in Erickson et al.[46] However, further studies are needed to assess the ideal dosage for ongoing daily use.

Compounded products were prepared from bulk substances to allow for exact dosing for study purposes and to allow for visually identical mixtures of gabapentin and placebo. While gabapentin is currently listed by the US FDA as a bulk drug substance currently under review,[47] due to its demonstrated benefits for situational anxiety for cats,[24,25] it was considered beneficial for use in this study. Veterinarians should adhere to compounding regulations and be aware that pharmacokinetic properties may differ between compounded and FDA-approved products.

Due to an inability to medicate some cats without restraint in the present study, some doses were missed. Statistically significant differences showing behavioral benefits of gabapentin were observed between treatment groups in PP analysis but only in CSS and LTE for ITT analysis. This suggested that some of the beneficial impacts of gabapentin for the treatment of fearful cats in shelters likely require that cats receive the majority (> 75% tested in the present study) of their 10-mg/kg gabapentin doses. While gabapentin was beneficial for cats that tolerated being medicated, forcefully medicating would likely reduce the benefits of gabapentin due to increased stress from handling[48] and the potential creation of negative associations with humans. Further research assessing the impacts of medication administration methods and its impact on behavioral progress would be beneficial.

No differences were observed between treatment groups for general in-shelter behavior; this was contrary to our hypothesis that gabapentin would decrease specific stress-related behaviors, such as overall percentage of time hiding. This may indicate that there were no general behavioral differences between treatment groups. Alternatively, the behavioral recording method, which was 1-hour time-lapse clips condensed into 5 seconds, may have resulted in too coarse of a behavior representation that could not determine differences between groups. Given that all other measures improved with adding gabapentin, the latter interpretation of the data may likely be warranted. Behavioral recording methods aiming to accurately monitor detailed behaviors over time would help determine finer-scale behavioral differences.

This research included some further limitations, including interpreting results from ITT and PP analysis. In PP analysis, the balance of randomization between groups may have been lost, while in ITT analysis, the actual effect of receiving the treatment was not directly tested.[43] Additional limitations existed, including that a control group for the BMOD program was not included for ethical

reasons. Therefore, this study did not test whether BMOD improved behavioral responses to humans or whether cats would have approached humans without behavioral intervention. However, based on evidence of behavior modification programs improving animal behavior goals,[15–17,49,50] the authors believe the BMOD program likely played a role in improving cats' response to humans. Further research experimentally testing the effects of BMOD and alternative BMOD approaches would be beneficial.

Due to the limited sample size, this study was not effectively powered for further analysis, such as the impact of medicine administration route and housing type on outcome measures. Additionally, further investigation of the impact of the method of administration of medication, how environmental variables impact BMOD progress, and other behavioral outcomes would be beneficial for informing the effective treatment of fearful cats in a shelter.

Overall, we conclude that daily gabapentin (10 mg/kg) was beneficial in behavior modification progress and improving signs of stress in shelter cats from HEs, and this research supports its use in shelters. However, most benefits of gabapentin likely require that cats receive the majority of their intended gabapentin doses. Results also show that fearful cats entering shelters from HEs can be ultimately treatable and adoptable in a shelter, regardless of gabapentin administration.

Supplementary Materials

Supplementary materials are posted online at the journal website: avmajournals.avma.org

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The authors have nothing to declare.

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