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Cats that get stressed when visiting the veterinary practice: can gabapentin help improve their welfare?

A Knowledge Summary by

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KNOWLEDGE SUMMARY

PICO question

In cats which are stressed as a consequence of veterinary interventions does gabapentin administration, compared with no gabapentin, result in lower levels of stress?

Clinical bottom line

There is moderate to good evidence to indicate that a single dose (100 mg) of oral gabapentin administered to cats might reduce signs of acute stress associated with veterinary visits. Two blinded, randomised, placebo controlled trials were reviewed, with consistency of direction of effect for the main outcome measure (Cat Stress Score) assessed.

Clinical Scenario

During a routine clinical audit of cat owner compliance with annual vaccination recommendations you notice that many cat owners do not attend the clinic annually for their cat's annual health check and vaccination. A post audit survey of non-compliant clients indicates that some owners are reluctant to bring their cat to the veterinarian unless the cat is unwell because their cat becomes visibly stressed and difficult to handle. You are keen to adopt measures that reduce stress in cats undergoing clinical examinations so that more clients may be compliant with your recommendations and your feline patients less stressed by the process. To this end you decide to review the evidence for pharmaceutical agents that may be beneficial in achieving this goal. One of the pharmaceutical agents that you review is gabapentin as you have anecdotally heard positive reports from other veterinary professionals with regards to its use for this purpose.

The evidence

Two randomised, double-blinded, placebo controlled clinical trials (van Haaften et al., 2017; Pankratz et al., 2018) addressed the PICO. One study (van Haaften et al., 2017) investigated the use of a single dose of gabapentin (100 mg) in pet cats, administered prior to exposure to transport and a veterinary examination. The other study (Pankratz et al., 2018) examined the use of a single dose of gabapentin (50 mg or 100 mg) in trapped community cats presented to a veterinary clinic for neutering. Both found a significant, stress reducing effect of gabapentin, although the primary outcome measures in both studies were subjective, qualitative ordinal behaviour based stress scores. No studies were identified that looked at the use of repeated dose gabapentin for management of stress over a longer time frame (e.g. during hospitalisation). Thus, there is moderate to strong evidence that gabapentin may be useful for reducing acute stress in cats stressed by veterinary interventions, but studies to demonstrate its efficacy as a pharmaceutical agent for reducing chronic stress in cats exposed to repeated or longer-term veterinary stressors are currently lacking.

Summary of the evidence

van Haaften et al. (2017)	
Population:	Healthy adult mixed breed pet cats that had previously shown signs of stress or difficult behaviour during veterinary examination or transportation.
Sample size:	20 cats

Intervention details:	Each cat was used as its own control, in a crossover, randomised, double-blinded clinical trial. Each cat had two veterinary clinic visits 1 week apart with either the gabapentin treatment or the placebo paired with each visit. 90 minutes prior to placing the cat into a cat carrier and departing for the veterinary clinic, the owner administered one of two treatments orally (either in a food treat or directly into the mouth): 1. Placebo (gelatin capsule containing 100 mg lactose powder) 2. Gabapentin (containing 100 mg gabapentin) The order in which each cat received the treatments was randomised, 11 cats received gabapentin on vet visit one, and nine cats received the placebo on visit one. After arrival at the veterinary clinic, each client waited 5 minutes before a standardised veterinary examination was performed. The hospital was closed to other appointments during these periods. The standardised examination was as follows: - The owner remained in view of the cat but did not interact with the cat during the examination. - The cat carrier was placed on the examination table for 1 minute. The cat was then given 2 minutes to exit the carrier on its own. If the cat did not exit on its own, it was gently removed by the veterinarian. - The same veterinarian and assistant performed each examination using gentle handling. - Heart rate and blood pressure was recorded. - The examination was prematurely ended if the cat tried to bite or scratch, or was assessed by the veterinarian as overly stressed. All evaluations were recorded on video and subsequently reviewed by two board certified veterinary behaviourists. The owners, veterinarian, and video observers were blinded to the treatments being administered. - Owners assigned a Cat Stress Score (CSS, Kessler & Turner, 1997) their cat's behaviour during: 1. Transportation to the veterinary clinic, and 2. The examination. - The veterinarian and assistant assigned a compliance score (CS, scale devised by the authors) to the cat's behaviour regarding ease of handling. - The video observers assigned a CSS, CS, sedation score (SS, Steagall et al. 2009), and aggression score (AS, scale devised by the authors) for each of the cats.

Study design:	Randomised, double-blinded, crossover trial
Outcome studied:	1. **Cat Stress Score** (Scale: 1–7, 1 = fully relaxed; 7 = terrorised) 2. **Compliance Score** (scale: 0–3, 0 = no resistance to handling; 3 = extreme resistance to handling ± elimination) 3. **Sedation Score** (scale: 0–4, 0 = no sedation, 4 = asleep/non-responsive to hand clap) 4. **Aggression Score** (scale: 0–2, 0 = no aggressive behaviours, 2 = attempt to bite/swat) 5. **Heart rate** (beats per minute) 6. **Blood pressure** - **Mean arterial pressure (MAP)** - **Systolic arterial pressure (SAP)** 7. **Adverse events** 8. **Miscellaneous observations** - Able to remove the cat from its carrier at the veterinary clinic - Able to complete the veterinary examination (including blood pressure and heart rate measurement)
Main findings: (relevant to PICO question):	1. **Cat Stress Score** - Owner-assessed CSS scores during transportation were significantly lower when cats received gabapentin as compared to when they received placebo (mean difference: -1.65, 95% confidence interval, Confidence interval (CI): -2.21 to -1.09, $P < 0.001$) - Owner-assessed ($P < 0.001$) but not video observer-assessed ($P = 0.06$) CSS scores during veterinary examination were significantly lower when cats received gabapentin as compared to when they received placebo. - The combined owner and video observer CSS during the veterinary examination showed a significant stress-reducing effect of gabapentin, after controlling for order effects, other fixed effects and individual variation (mean difference: -0.69, 95% CI: -0.99 to -0.39, $P < 0.001$), as compared to the placebo. 2. **Compliance Score** - Veterinarians and video observers reported that cats

	were easier to handle when gabapentin was administered (≤ 0.02) as compared to the placebo. - The combined veterinarian and video observer examination CS showed a significant stress reducing effect of gabapentin (mean difference: -0.41, 95% CI: -0.61 to -0.20, P < 0.001) as compared to the placebo. **3. Sedation Score** - Cats had a significantly higher SS when gabapentin was administered (mean difference: 0.42, 95% CI: 0.22 to 0.62, P < 0.001) as compared to placebo. **4. Aggression Score** - Cats had a significantly lower AS when gabapentin was administered (mean difference: -0.18, 95% CI: -0.26 to -0.09, P < 0.001) as compared to the placebo. **5. Heart rate** - Univariate analysis indicated no effect of treatment upon heart rate during examination. However, after controlling for other fixed effects, order effects and individual variation, the heart rate was significantly lower when gabapentin was administered (mean difference: -15.2, 95% CI: -29.5 to -0.8, P = 0.04). **6. Blood pressure** - **MAP** There was no significant effect of treatment on MAP. - **SAP** There was no significant effect of treatment on SAP. **7. Adverse events** - Adverse effects were not noted in cats administered the placebo. - Six cats administered the gabapentin exhibited adverse effects. Two cats vomited after 60 minutes, with a further one cat exhibiting signs consistent with nausea (hypersalivation and lip licking). A further three cats exhibited clinical signs during the examination: mild muscle twitching (n = 2) and unequal pupil size (n = 1). - Owner home reports were available for 15 of the 20 cats. Of these 15 cats, after receiving the gabapentin treatment, 12 appeared sedated on arrival home (three markedly so), six of these also exhibited ataxia. Four cats were more friendly than usual, with one cat showing a reduction in fear to dogs. All clinical signs reported were temporary, and had disappeared within 8 hours of gabapentin administration. **8. General observations relevant to the information below and the PICO.** - The examination was able to be completed in 19 cats after receiving gabapentin.

	- The examination was not able to be completed in four cats after receiving the placebo. - The examination was not able to be completed in one cat after receiving gabapentin or the placebo.
Limitations:	- Small sample size - Inter-observer agreement between video observers (veterinary behaviour experts) was poor for CSS, CS, and SS. - Inter-observer agreement was only fair (Cohen k: 0.40–0.59) between the observers who assessed CSS via video and the owners who assessed CSS during the examination (score 0.46), and poor (Cohen k:<0.40) between the observers who scored CS via video and the veterinarian who assessed CS during the examination (score 0.36). Nb. The Cohen's kappa statistic is a commonly used statistical test designed to assess inter-rater reliability and is important in that in assesses the extent to which the data collected represents the variable being measured (McHugh, 2012). - The methods report that an assistant (as well as the veterinarian) assigned a CS to each cat but this data does not appear in the results section.
Pankratz et al. (2018)	
Population:	Unowned community cats estimated to be 4 months or older, healthy or with mild injuries or mild systemic disease (ASA* grade I / II), and presented to the neutering facility in a humane cat trap. *American Society of Anesthesiologists
Sample size:	53 cats (56 were enrolled, but 3 had an ASA score of III+ when examined under anaesthesia so were excluded at that point)
Intervention details:	This was a randomised block, placebo controlled, double-blinded trial. There were three treatment groups: 1. Placebo (n = 19) 2. Low dose gabapentin (50 mg) (n = 17) 3. High dose gabapentin (100 mg) (n = 17) Gabapentin was administered in a standardised suspension product, with the formulation adjusted to standardise the oral dose to 1 ml for each cat. Placebo cats were given the suspension only. All doses were supplied orally via a syringe/catheter, with the cat trapped into one of end of the cat trap/cage. The timeline was as follows: - Cats were brought to the neuter facility in traps by local trap-neuter-return volunteers. They were kept in these single cat traps and covered with a cloth except when it was necessary to observe the cat for the purpose of the study. - Cats were screened between 5–6pm. The time

	between admit and screening was not defined. - 30 minutes after screening a baseline measurement was taken, followed by the treatment (placebo or high/low dose gabapentin). - Cats were then observed for the next 12 hours. They were fasted during this period. Study measurements were taken during this period. - At the end of the study observation period they were anaesthetised, clinically examined and neutered if entire. The relevant data time points are: - Screening - 30 minutes after screening: baseline assessment (pretreatment) - 0h (cats treated according to treatment group) - 1h post treatment - 2h post treatment - 3h post treatment - 12h post treatment - Post 12h (variable time point) whilst under anaesthesia A veterinarian blind to treatment and not involved in study data collection allocated cats to treatment groups (1, 2, 3) and administered the respective treatment. The veterinarian screening the cats was also blinded. It is not reported who analysed the data and if this was done with the analyst blinded.
Study design:	Randomised block, placebo controlled, double-blinded trial
Outcome studied:	The outcome variables were: 1. **Cat Stress Score** (CSS, Kessler and Turner, 1997) - (Scale: 1–7, 1 = fully relaxed, 7 = terrorised) 2. **Global Sedation Score** (GSS, adapted from Hopfensperger et al. 2013) - (Scale: +3 to -3, +3 = very sedated, 0 = normal, -3 = very excitable) 3. **Respiratory rate** 4. **Facial Injury Score** (FIS, scale devised by the authors) - (Scale: 0–4 , 0 = no injuries, 4 = severe injuries) 5. **Adverse events** Outcome measures 1, 2 and 3 were measured at baseline, 1h, 2h, 3h and 12h post treatment. Outcome measure 4 was measured at baseline, 12h and while under anaesthetic. Outcome measure 5 timing was not formally reported but presumed

	to be continuous due to the nature of the outcome.
Main findings: (relevant to PICO question):	**Only the findings directly relevant to the PICO are reported here.** 1. **Cat Stress Score** - Compared to the placebo group, cats in the low dose gabapentin group had a significantly lower CSS at 2h (P = 0.035) and 3h (P = 0.029). - Compared to the placebo group, cats in the high dose gabapentin group had a significantly lower CSS at 2h (P = 0.029) and 3h (P = 0.020). - There was no significant difference in CSS between the high and low dose gabapentin groups (P = 0.79). - Treatment means (± standard error of the mean, S.E.M.) are reported as figures, so exact figures cannot be reported here so the reader is urged to obtain the paper to visualise effect size. 2. **Global Sedation Score** - There was no treatment effect or treatment by time effect on GSS. 3. **Respiratory rate** - Compared to the placebo group, cats in the high dose gabapentin group had a significantly lower respiratory rate at 1h (P = 0.03) but not at 2h (P = 0.07) or 3h (P = 0.80). - There were no significant differences at any time point between cats in the placebo and low dose gabapentin groups. 4. **Facial Injury Score** - The authors state that FIS were not sensitive to detection over time; therefore, the injury scores were not used in statistical analyses. 5. **Adverse events** - No adverse effects that were unique to cats administered gabapentin were identified. - Four cats hypersalivated 1h post-administration of treatment (placebo: n =2; low dose gabapentin: n = 1; high dose gabapentin: n = 1), with resolution of clinical signs by 2h post-administration. - No other adverse effects were noted.
Limitations:	- Small sample size - No description of how the CSS scores of “terrorised, very fearful, etc.” were assessed. Only one person was used to assess/score the cats and they were trying to assess this by looking into a cat trap. - The GSS used was designed for use with dogs. - Length of time between entry into the facility and screening time is unclear.

Appraisal, application and reflection

There is moderate to good quality evidence from two randomised, controlled, double-blinded studies (van Haaften et al., 2017; Pankratz et al., 2018) to indicate that the use of oral gabapentin can be beneficial in the short-term reduction of stress in cats exposed to acute stressors associated with the veterinary clinic. One potential weakness relevant to both studies was that Cat Stress Score (CSS), as the main stress assessment tool used, showed poor or fair inter-observer reliability (only assessed by van Haaften et al., 2017). However, blinded observers scored the cats and the direction of any effect was similar, suggesting that this was not a serious issue when determining whether gabapentin had an effect (just the magnitude of the effect). Additional objective physiological measures to support the behavioural observations would have further strengthened confidence in the findings reported by each of the studies. However, the behavioural findings are supported by a reduction in heart rate (van Haaften et al., 2017) or respiratory rate (high dose only, preceded behavioural reduction, Pankratz et al., 2018).

Both studies found that a single dose size of 100 mg/cat was associated with a reduction in the levels of behavioural parameters associated directly or indirectly with feline stress, and this effect was observed 90–180 minutes post administration of the gabapentin. A similar effect was observed both in pet cats given gabapentin prophylactically (pre-stressor) and in unowned community (not pet) cats given gabapentin once already showing a behavioural stress response. However, there is some evidence (Pankratz et al., 2018) to suggest that a lower dose of gabapentin may be sufficient, with 50 mg/cat also being associated with a significantly lower CSS (but not respiratory rate) than control cats, but not significantly different from the high dose 100 mg/cat group.

Whilst the Pankratz et al. (2018) study population was unowned community cats, the reported CSS of both control and experimental group cats was similar in both studies, which might suggest that a similar behavioural state and effect was observed. This may be relevant to the veterinary professional seeking to minimise any unwanted side effects of the medication (none in Pankratz et al., 2018; ataxia, sedation, and vomiting/hypersalivation in van Haaften et al., 2017) or considering repeated doses. No studies were found that examined the use of repeated dosing of gabapentin on feline stress levels within the clinic, but the dose (high, low, control) plotted against time (1h, 2h, 3h) graph in Pankratz et al. (2018) suggests a relatively short-lived effect. This may limit clinical application for longer duration stressors (e.g. during hospitalisation periods), and further research to determine multiple dose efficacy or safety over longer-term stressor exposure would be useful. In the interim, the usefulness of single dose gabapentin to hospitalised cats could be improved by judicious use of procedure planning to allow potentially stressful clinical procedures to be performed, where possible, within the 90–180 minute period post dosing.

Methodology Section

Search	
Databases searched and dates covered:	Pubmed (1970 – 14/04/2019); Web of Science (1970 – 14/04/2019); CAB Abstracts on OVID Platform (1973 – Week 14 2019)
Search strategy:	PubMed: (cat or cats or feline or felis or felid) and (gabapentin) and (scared or reactive or reactivity or emotion or emotional or fear or fearful or stress or stressed or anxious or anxiety or behaviour) Web of Science: (cat or cats or feline or felis or felid) and (gabapentin) and (scared or reactive or reactivity or emotion or emotional or fear or fearful or stress or stressed or anxious or anxiety or behaviour) CAB Abstracts: (cat or cats or feline or felis or felid) and (gabapentin) and (scared or

	reactive or reactivity or emotion or emotional or fear or fearful or stress or stressed or anxious or anxiety or behaviour)
Dates searches performed:	Date search performed 14/04/2019 (all databases)

Exclusion / Inclusion Criteria	
Exclusion:	Pre-defined exclusion criteria: non-English language, popular press articles, narrative reviews, conference abstracts
Inclusion:	Systematic reviews; any comparative (control group utilised) study in which the effect of prophylactic oral gabapentin on preventing or reducing stress, fear and anxiety in cats was studied.

Search Outcome

Database	Number of results	Excluded – did not address the PICO	Excluded – not English language	Excluded – conference abstract only	Excluded – duplicate	Total relevant papers
Pubmed	5	3	0	0	0	2
Web of Science	12	10	0	0	2	0
CAB Abstracts	9	6	0	1	2	0
Total relevant papers when duplicates removed						**2**

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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