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Daytime and nocturnal activity in treated dogs with idiopathic epilepsy compared to matched unaffected controls

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Abstract

Background: In dogs, antiepileptic drugs (AED) cause lethargy but quantitative data regarding the effects of AED on activity levels are not available, and little is known about how AEDs affect sleep quality.

Objective: To quantitatively compare activity levels and nocturnal activity in dogs previously diagnosed with idiopathic epilepsy (IE) receiving AEDs compared to age- and breed-matched control dogs.

Animals: Sixty-two dogs with IE and 310 control dogs.

Methods: This is a 3-month prospective parallel observational study. An activity monitoring device for dogs was used to measure daily activity levels and sleep scores in all dogs.

Results: Dogs with IE treated with AEDs had an 18% average lower baseline activity level compared to control dogs ($P = .005$; point estimate = 0.82, 95% confidence interval [CI], 0.75-0.90). The combination of phenobarbital and potassium bromide (KBr) was associated with an average 28% decrease in activity in dogs with IE compared to control dogs ($P = .03$; point estimate = 0.72; CI, 0.62-0.82). Mean sleep scores were not significantly different in dogs with IE receiving AEDs compared to control dogs ($P = .43$). However, higher dosages of KBr were associated with lower sleep scores ($P = .01$).

Conclusions: Dogs with IE receiving AEDs have lower activity levels, but no difference in sleep scores, compared to controls. The combination of phenobarbital and KBr had the largest decrease in activity between groups. Higher doses of KBr may affect nocturnal activity in epileptic dogs.

KEYWORDS
antiepileptic drugs, canine activity monitoring device

1 | INTRODUCTION

Idiopathic epilepsy (IE) is a common neurologic condition in dogs, and currently, antiepileptic drugs (AEDs) are the mainstay of treatment.

Abbreviations: AED, antiepileptic drug; ANOVA, analysis of variance; App, application; CAMD, canine activity monitoring device; EEG, Electroencephalography; CI, confidence interval; IE, Idiopathic epilepsy; KBr, potassium bromide; REM, rapid eye movement; S-W, sleep-wakefulness.

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Adverse effects, including sedation, lethargy, and decreased activity, are well documented with the use of all AEDs used to treat seizures in veterinary medicine.[1] These specific AED adverse effects can negatively impact the owner's perception of quality of life in their epileptic dogs.[2] In the human medical literature, people with epilepsy are 1.4 times more likely to be physically inactive compared to the general population.[3] Specifically, phenobarbital and higher doses of levetiracetam are significantly associated with more daytime drowsiness and inactivity compared to other AEDs, such as zonisamide.[4] However, in dogs, quantitative data are lacking to inform owners of the effects of AED treatment on their dog's activity level.

People with epilepsy are also more likely to have sleep disturbances, and less sleep makes seizures more likely.[5] Adults with epilepsy, whether receiving AEDs or not, are twice as likely as controls to have sleep disturbances, including insomnia, sleep apnea, restlessness, and rapid eye movement (REM) sleep disorders and to have lower perceived quality of life because of these sleep disturbances.[6-8] Children with epilepsy are 10 times more likely to have sleep disturbances compared to age-matched children without epilepsy.[9] In veterinary medicine, little is known about how epilepsy and AEDs impact sleep quality.

We hypothesized that dogs with IE treated with AEDs would have lower activity levels and poorer sleep scores compared to age- and breed-matched control dogs. The specific aim of our study was to quantitatively compare activity levels and nocturnal activity in dogs previously diagnosed with IE receiving AEDs compared to age- and breed-matched unaffected and untreated control dogs.

2 | MATERIALS AND METHODS

The study design was a prospective clinical observational study with an intent-to-treat analysis over a 12-week period. The protocol was approved by the Institutional Animal Care and Use Committee at the University of Wisconsin—Madison, School of Veterinary Medicine. Owners gave informed consent for their dogs to be enrolled as study participants.

2.1 | Study population

Dogs with IE between the ages of 1 and 9 years, of any breed, sex, or weight were recruited by e-mail and social media platforms. Dogs needed to have presumptive or confirmed IE using tier I or tier II criteria as described by the International Veterinary Epilepsy Task Force Consensus Proposal.[10] Dogs needed to have a seizure history of at least 1 year, >2 generalized seizures in their lifetime, and a seizure frequency of >1 seizure every 3 months in the 6 months before enrollment. Dogs must have been receiving at least 1 AED or any AED drug combination for >6 months. Dogs were excluded if they had other clinically relevant co-morbidities that could affect activity level.

The control group was derived from a database of activity data from over 1 million dogs maintained by the manufacturer of the canine activity monitoring device (CAMD) used in this study (FitBark, Kansas City, Missouri). Technical support for the CAMD searched the database to identify 5 dogs with the same age and breed as each epileptic dog enrolled in the study, for a total of 310 dogs. For inclusion criteria for the control dogs, no preexisting medical conditions or medications could be listed in the dog's profile information. For mixed breed dogs, the main breed was used to match dogs (eg, Shepherd mix). The season and time period for data acquisition (12 weeks) also were matched with cases to avoid potential bias from seasonal differences in activity.

At the time of enrollment, all qualifying criteria were confirmed by the study investigator. Intake forms were completed by the owners with detailed information regarding the dog's seizure history, seizure frequency, AED medications (including drug name, dose, and frequency), rescue protocols, other medications or supplements regularly administered, regular routine (including sleep schedule), and food (brand and amount per day).

2.2 | Activity monitoring and sleep score

A CAMD was attached to the dog's collar. The CAMD uses a 3D accelerometer to track activity levels and takes multiple readings per second, which are then stored in 1-minute data segments.[11] Constant accelerations, such as gravity, are filtered out using an algorithm so as to make the data collected more accurate.[12] The activity information is quantified as number of recorded movements per minute (called Bark Points, referred to here as activity points). The device transmits data to a paired smartphone using Bluetooth (Bluetooth SIG, Kirkland, Washington) technology.

Nocturnal activity (restlessness) was used as a surrogate of sleep quality. Sleep score was calculated by the device as the percentage of time spent restless over a 4-hour window, which was set by the investigator at the time of enrollment based on the owner's normal sleep schedule. For example, if a dog was restless for 1 hour over the 4-hour window, then the sleep score would be 75%. The same study team members recorded all data entries, including activity monitoring and sleep scores, for the 12-week period. For control dogs, the owner chose the 4-hour window to monitor sleep when setting up the application (app) on their smartphone.

Each owner downloaded the CAMD manufacturer's app to their smartphone, enrolled his or her dog using the app, and registered our hospital as the contact veterinarian. This allowed our study team to have continuous access to the dog's data on the manufacturer's website. Owners were instructed to leave the CAMD on the collar and to leave the collar on the dog except for baths or swimming. They were asked to synchronize the CAMD to their smartphone or tablet by opening the app at least 1 time per week (or more).

2.3 | Outcome measures and statistical analyses

The aim was to recruit 80 client-owned dogs with IE. This study was part of a larger interventional project evaluating the effects of exercise on seizure frequency in dogs and was powered for those outcomes. Activity (recorded as activity points) and sleep (recorded as sleep score) were obtained weekly from the CAMD manufacturer's website and recorded by a study team member. The primary outcomes used in

analysis were weekly averages of daily activity points and weekly averages of daily sleep scores over the 3-month study period for each dog.

The primary method for detecting statistically significant differences in outcomes was a 2-way analysis of variance (ANOVA) with factors for treatment group (idiopathic epileptic dogs receiving AEDs vs matched controls) and match index (1 match index for each epileptic dog and its 5 matched controls). To evaluate whether the average outcome among dogs in the treatment groups was different than the outcome among dogs in the control group, we performed an *F* test on the treatment group factor in this ANOVA model. If significant differences were found in the mean outcomes of the 2 groups from the previous *F* test, we estimated the percentage increase or decrease between the epileptic dogs and their age- and breed-matched controls. This estimate was derived from the ratio of mean outcomes between the 2 groups. The 95% confidence interval (CI) for this ratio was calculated from a bootstrap procedure using the percentile method to account for the ratios potentially arising from a skewed distribution.

3 | RESULTS

3.1 | Study population

In total, 82 epileptic dogs were enrolled in the study. One owner never synchronized to the app, and this case was excluded. Eight dogs had not completed the study at the time of data analysis and were excluded. In addition, for another 8 dogs, the CAMD manufacturer did not have 5 controls of the same age and breed available, and these paired data were not used in the analysis. Three dogs had AED discontinued treatment during the study and also were excluded. Therefore, data from 62 dogs were available and paired with 5 control dogs each (310 control dogs) from the CAMD database. During the 12-week study period, 2 dogs were euthanized, 1 because of liver failure and 1 because of worsening seizures, at 8 weeks and 11 weeks into the study, respectively. In addition, 1 owner was concerned that the CAMD may have been causing an increase in seizure frequency and removed her dog from the study after 6 weeks. For these 3 cases, at least 1 month of data were present, and therefore, these cases were included in the analysis.

Of the epileptic dogs, breeds included: mixed breed (n = 18), Australian Shepherd (n = 7), Border Collie (n = 6), Labrador Retriever (n = 5), Cocker Spaniel (n = 2), Golden Retriever (n = 3), Goldendoodle (n = 3), English Springer Spaniel (n = 3), Cavalier King Charles Spaniel (n = 2), French Bulldog (n = 2), German Shorthair Pointer (n = 2), German Shepherd (n = 2), and 1 each of Beagle, Welsh Corgi, English Labrador, English Mastiff, Great Pyrenees, Shiba Inu, and Vizsla. There were 16 spayed females, 36 neutered males, and 10 intact males. The average weight was 26.8 kg (range, 5-91 kg). The mean age at the time of enrollment was 4.47 years (range, 1.3-8.3 years) and the mean age at the time of first seizure was 2.58 years (range, 0.3-7.0 years).

Overall, 22 dogs received 1 AED, 16 dogs received a combination of 2 AEDs, 19 received a combination of 3 AEDs, and 5 dogs received a combination of 4 AEDs. Information regarding dosing information, including mean and ranges for each AED, is presented in Table 1.

3.2 | Activity

Dogs with IE treated with AEDs had significantly lower baseline activity (mean, 6710 activity points; SD, 2514) compared to unaffected, untreated control dogs (mean, 8208 activity points; SD, 3497, $P = .005$; Figure 1). The point estimate was 0.82 when comparing all dogs with IE treated with AEDs compared to control dogs, interpreted as an 18% decrease in activity. The 95% CI for the ratio between groups was 0.75 to 0.90, or an 10% to 25% decrease in activity for dogs with IE treated with AEDs compared to the control dogs.

In a subgroup analysis, we compared dogs with IE treated with phenobarbital (with or without other AEDs but without KBr), KBr (with or without other AEDs but without phenobarbital), or a combination containing both phenobarbital with KBr (Table 2). The only subgroup that was associated with a statistically significant decrease in activity in dogs with IE compared to control dogs was the combination containing both phenobarbital and KBr ($P = .03$). The point estimate was 0.72 for epileptic dogs receiving this specific medication combination compared to control dogs, interpreted as a 28% decrease in activity. The 95% CI of this specific combination was 0.62 to 0.82, or an 18% to 38% decrease in activity in dogs with IE compared to control dogs. In this group of 14 dogs, all epileptic dogs had lower activity than their matched control dogs (Figure 2).

A separate analysis was performed among epileptic dogs to determine if the dosage of AEDs in mg/kg was associated with decreased

TABLE 1 Daily dosages of antiepileptic drugs in mg/kg/d in 62 dogs with idiopathic epilepsy evaluated for activity levels and sleep scores over a 3-month period

Drug	Number of dogs (n)	Mean Dose (mg/kg/d)	SD	Range (mg/kg/d)
Phenobarbital	46	6.4	2.6	1.4-13.7
Potassium bromide	19	36.3	14.2	9.5-64.9
Zonisamide	21	15.2	6.6	2.5-25.9
Levetiracetam—intermediate release	20	119.9	49.7	42.4-258.6
Levetiracetam—extended release	20	66.4	26.2	29.0-120.0
Gabapentin	2	21.1	14.8	10.6-31.6
Topiramate	2	26.0	9.9	19.0-33.0
Imepitoin	1	20.8	N/A	N/A

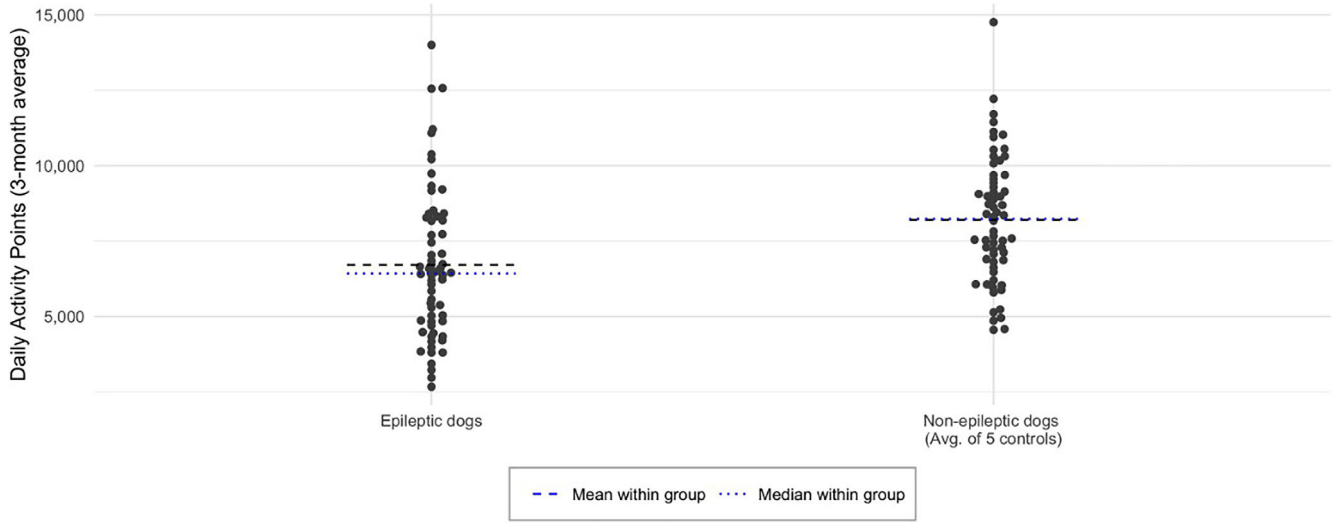

FIGURE 1 Scatterplot of 3-month averaged daily activity levels in 62 treated dogs with idiopathic epilepsy (IE) assessed with accelerometry collars, compared to data from 310 breed- and age-matched unaffected, untreated control dogs from the manufacturer's database ($P = .005$ between groups). Dogs with IE had a mean activity level of 6710 activity points compared to a mean of 8208 activity points for control dogs

TABLE 2 A 2-way ANOVA was used for comparison of 3-month averaged activity levels in 62 dogs with IE treated with different AED combinations, compared to data from 310 breed- and age-matched unaffected, untreated control dogs

Drug combinations	Number of dogs	Ratio of activity (treated epileptics vs unaffected control dogs)	95% Confidence interval	Difference in activity compared to control dogs	*P* value
All AED combinations	62	0.82	0.75-0.90	10%-25% decrease	**.005**
Combinations containing phenobarbital and KBr	14	0.72	0.62-0.82	18%-38% decrease	**.03**
Combinations including phenobarbital without KBr	32	0.86	0.73-0.95	5%-27% decrease	.07
Combinations containing KBr without phenobarbital	6	1.07	0.78-1.45	22% decrease-45% increase	.77
Zonisamide and/or levetiracetam without phenobarbital or KBr	10	0.82	0.64-0.96	4%-36% decrease	.09

Note: The reported *P* value is from the *F* test for differences in dogs with IE versus control dogs. The 95% confidence interval for this ratio was calculated from a bootstrap procedure. Other drugs in the AED combinations included: zonisamide, levetiracetam, gabapentin, topiramate, and imepitoin. *P*-values in bold are statistically significant.
Abbreviations: AED, antiepileptic drug; ANOVA, analysis of variance; IE, idiopathic epilepsy; KBr, potassium bromide.

activity among the 62 dogs with IE in the study. A multiple regression relating the response of interest (3-month activity point average) with all AED dosage information and control variables (age and indicators for spayed females, neutered males, and intact males) was performed. No AED significantly affected the 3-month activity point activity score average in any of the regressions performed (results not shown).

3.3 | Sleep

Contrary to our hypothesis, mean sleep scores over 3 months were not significantly different in dogs with IE receiving AEDs (mean, 84.6%; SD, 4.8%) compared to control dogs (mean, 83.6%; SD, 7.8%; $P = .43$; Figure 3). In addition, when a subgroup analysis was performed comparing different AED combinations, no statistical significance was detected between the groups (phenobarbital and KBr [with or without other AED], $P = .46$; phenobarbital [with or without any other AED] and no KBr, $P = .53$; KBr [with or without other AED] and no phenobarbital, $P = .17$; no phenobarbital or KBr, $P = .53$).

When considering whether medication dosages affected 3-month sleep scores among the 62 study dogs in a multiple linear regression model, higher doses of KBr were linearly correlated with lower sleep scores (ie, more nocturnal activity), which was statistically significant ($P = .01$; Figure 4). No other AEDs had statistically significant correlations between dosage and sleep score.

4 | DISCUSSION

Idiopathic epilepsy is the most common cause of seizures in dogs and is the most common chronic medical condition in dogs managed by veterinary neurologists. Antiepileptic drugs are the current mainstay

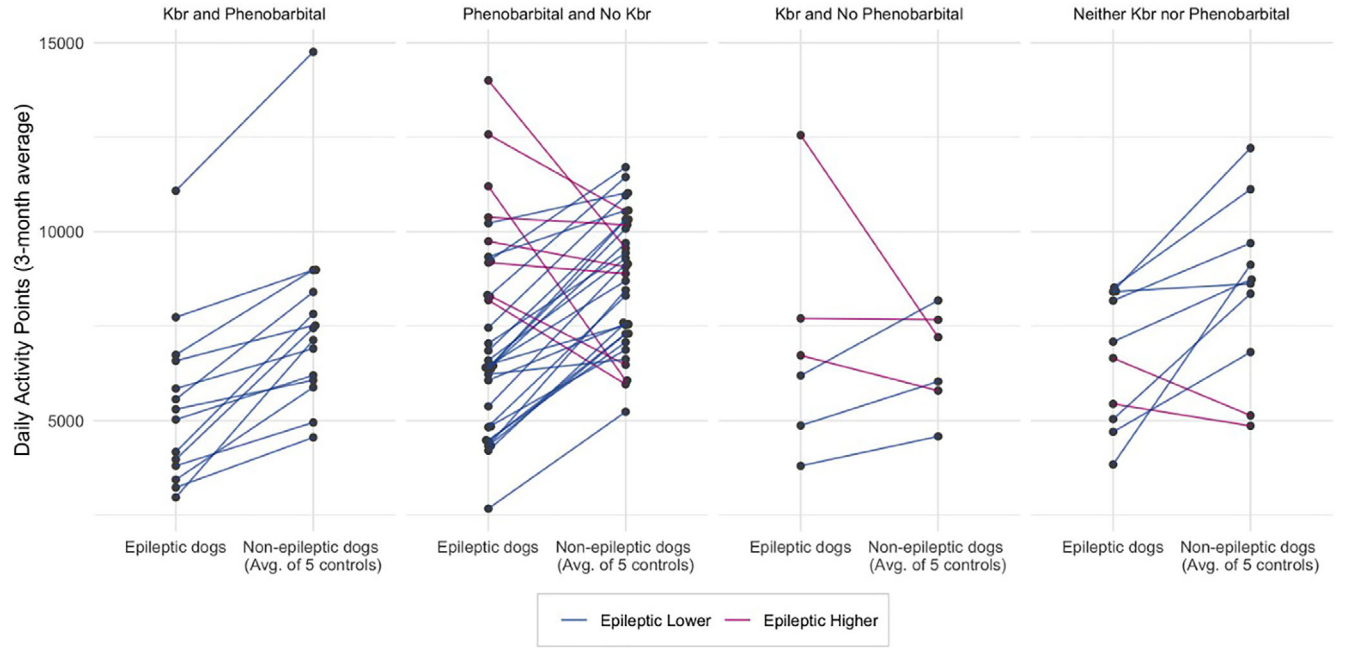

FIGURE 2 Slope chart displaying subgroup analysis of activity levels for different antiepileptic drugs (AED) combinations in dogs with idiopathic epilepsy (IE) compared to control dogs. Each line represents 1 dog with IE and the average activity of the 5 matched control dogs. Blue lines correspond to the dog with IE having a lower activity level than the controls. Pink lines correspond to the dog with IE having a higher activity level than the controls

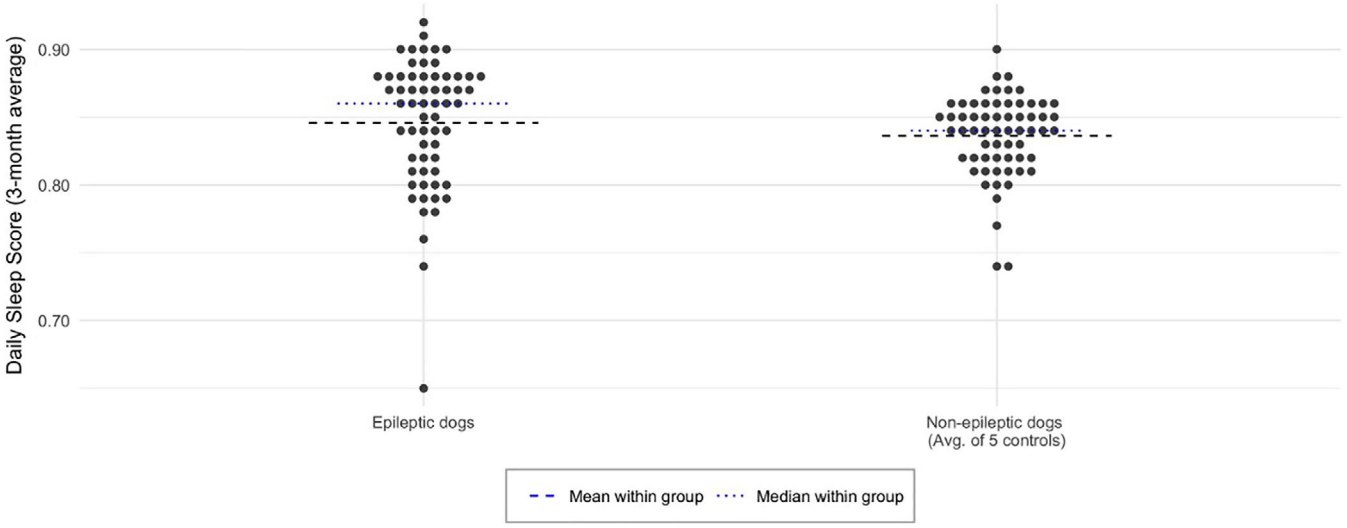

FIGURE 3 Scatterplot of 3-month averaged nightly sleep scores in 62 treated dogs with idiopathic epilespy assessed with accelerometry collars, compared to data from 310 breed- and age-matched unaffected, untreated control dogs from the manufacturer's database. The mean sleep scores of epileptic dogs receiving antiepileptic drugs (AED) therapy (84.6%) was not significantly different than sleep score of age- and breed-matched control dogs (83.6%; $P = 0.49$)

of treatment, but very little quantitative information is currently available regarding the effect of AEDs on activity and sleep in dogs. Our study found a significant decrease in activity levels in dogs with IE being treated with AEDs compared with age- and breed-matched control dogs, which is consistent with findings in human medicine. Studies of people with epilepsy have documented a significant decrease in normal activity levels compared with a control population.[3,4] Our study is the first study to quantify the level of activity in dogs with IE being treated with AEDs. In our study, dogs with IE receiving the combination of phenobarbital and KBr had significantly lower activity levels compared to age- and breed-matched control dogs. For sleep scores, no significant differences were detected between the epileptic and control dogs. However, a correlation between higher doses of KBr and lower sleep scores was found when considering epileptic dogs in our study.

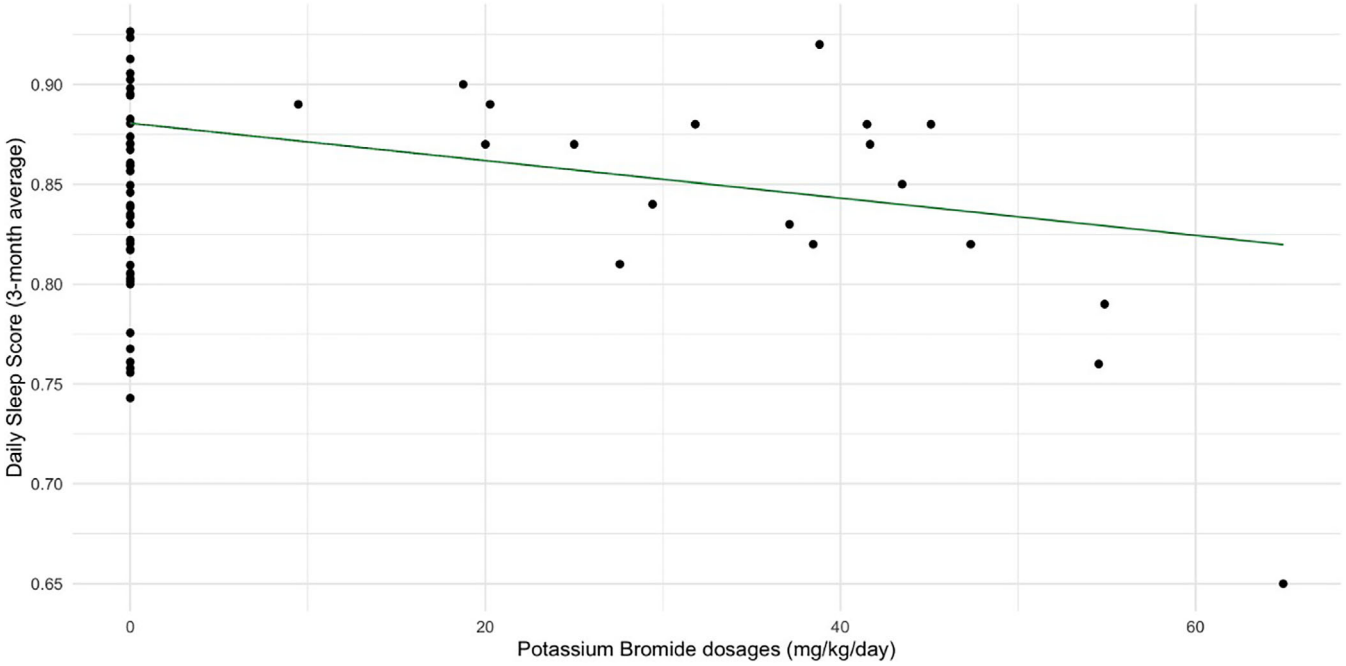

FIGURE 4 Linear regression model of dogs with idiopathic epilepsy showing relationship between dosage of potassium bromide (KBr) and the 3-month average sleep score. This model includes covariates for age, sex, and all antiepileptic drugs (AED) dosages. The green line shows sleep score predictions for a range of KBr dosages, averaged over the other covariates, and indicates higher dosages of KBr are associated with lower sleep scores (ie, more restlessness)

Several studies have been conducted regarding perception of quality of life by caregivers (owners) of dogs with epilepsy.[2,13,14] All of these studies have determined that sedation, lethargy, and increasing sleepiness have been correlated with owner perception of decreased (ie, poorer) quality of life in epileptic dogs receiving AEDs. In addition, a recent meta-analysis indicated that sedation and lethargy were some of the most common clinical signs and adverse effects of the AEDs used to treat seizures in veterinary medicine.[1] Although a commonly reported adverse effect, the quantitative difference in activity has not been reported previously in veterinary medicine. This point is important in counseling owners and being able to provide realistic expectations and a quantitative level of expected decrease in activity. In addition, this information is helpful when determining what AEDs may fit the dog and owner's lifestyle. For example, because the combination of phenobarbital and KBr cause a substantial decrease in activity level, it may be beneficial to avoid this combination in working or agility dogs, or other situations in which a dog is expected to perform.

There is a strong and complex relationship involving epilepsy and sleep that is considered bidirectional; a lack of sleep can provoke seizures and people with epilepsy have poorer sleep quality.[5] People with epilepsy (whether receiving AED therapy or not) have significantly impaired sleep quality compared to controls.[15] Sleep is not routinely studied in veterinary medicine, and even recent studies rely on owner observation for measuring sleep, which may be inaccurate.[16] Many studies involving sleep in humans, especially sleep quality, involve questionnaires and participant impressions and reflections on restfulness after sleeping. This subjective assessment is not possible in veterinary medicine, and even using video-based assessments of sleep may not be accurate because a dog may appear to be sleeping when it is not.

Electroencephalography (EEG) also is used to objectively evaluate sleep in human medicine, but EEG studies are limited in veterinary medicine by availability and patient cooperation. One study evaluated EEG during sleep in 4 Beagles with IE compared to control dogs without epilepsy.[17] No difference was detected in the percentage of time spent in the different sleep-wakefulness (S-W) stages, but the epileptic dogs had shorter S-W epochs, as well as shorter REM and deep slow wave sleep latencies, suggesting that differences in sleep patterns exist in dogs with IE compared to control dogs. Interestingly, no difference in sleep patterns was found among the AEDs used (diazepam, phenytoin, flunarizine, and phenobarbital) but only 4 dogs were evaluated, limiting the power of the study. Using EEG as a tool to study sleep in a larger number of dogs with IE compared to control dogs could be a useful next step as a more quantitative measurement of sleep.

Contrary to our hypothesis, no statistically significant difference in sleep score was found in dogs with IE receiving AEDs compared to the control dogs. However, when AED dose and drug type were considered, dogs receiving higher doses of KBr had lower sleep scores (ie, were more restless) than dogs receiving other AEDs. Potassium bromide works by substituting for chloride, and specifically in the central nervous system, it may replace as many as 30% of chloride ions. Interestingly, as the concentration of bromide increases, it causes a more depressant effect in the membrane, which in theory should lead to

improved sleep scores.[18] Potassium bromide is no longer used to treat people with epilepsy, and therefore has not been included in clinical or meta-analysis studies in the human medical literature, but other AEDs have been associated with more restless sleep, including phenobarbital and higher doses of levetiracetam.[4] Phenobarbital and higher doses of levetiracetam have been associated with shorter REM and longer S-W sleep cycles in people, but effect of KBr on nocturnal activity or sleep quality has not been assessed previously in human or veterinary medicine. Dogs with IE receiving higher doses of KBr may have more difficult to control seizures or more poorly controlled IE, which could have affected the sleep scores obtained in our study. Previous research has associated more clinical signs (termed bromism) associated with higher doses and concentrations of KBr in dogs, but changes in sleep were not considered.[19]

In our study, an accelerometer designed for dogs was used to measure each dog's activity level and sleep score. This device has been specifically adapted for dogs and designed to be worn on a collar. Algorithms have been implemented to remove constant forces, such as gravity, so as to improve accuracy. The activity was quantified by activity points, as "steps" were inappropriate because the device was not worn on a limb. Previous studies evaluating the accuracy of accelerometers in dogs have shown that it does not matter if the device is worn on a collar or a harness,[20] but differences were shown when walking a dog if the accelerometer was attached to a collar or harness that was directly attached to a leash.[21] With regard to sleep, the device has not been evaluated for determining sleep quality in dogs. We cannot say that restlessness necessarily correlates with poorer sleep quality in dogs, which is why the term nocturnal activity was used as a surrogate in our study. In addition, it is common for dogs to be awake, but not necessarily moving, and this lack of movement would be classified as sleeping by the CAMD. Using an accelerometer does allow for a more quantitative assessment of sleep in dogs compared to owner observations alone, as well as allowing for a normal routine (ie, the owner does not need to be awake during the night to monitor sleep).

Our study had several limitations. Our current study was part of a larger study on the effects of exercise on seizure frequency, which is why these particular inclusion criteria were used. For example, we chose a more refractory population of dogs, with dogs needing to be on AEDs and still having a seizure frequency of at least 1 seizure every 3 months. This inclusion criterion meant that our population of dogs with IE was more refractory than the average population of dogs with IE. In general, in dogs with IE, 25% to 30% are considered refractory and need >1 medication.[22,23] In our population, 40 of 62 dogs (64.5%) were receiving ≥ 2 AEDs as maintenance treatment. Therefore, our sample population had fewer cases (with less power) to evaluate the effect of a single AED on activity level.

In addition, the activity level of the dog often is linked directly to owner activity. Owner enrollment in a study can affect behavior, which may affect results. Weekly averages were used to normalize daily fluctuations in activity and 12 weeks were evaluated to normalize any possible initial change in activity after enrollment. The weekly averages help normalize daily fluctuations, but do not help for other potential scenarios, such as the dog being kenneled or a family vacation involving more activity. Lastly, all dogs with IE were receiving AEDs in our study, and therefore, we could not determine the impact of IE alone on activity levels and sleep compared to control dogs.

In conclusion, our study quantitatively showed a statistically significant decrease in activity level in dogs with IE receiving AEDs compared to age- and breed-matched controls. Specifically, the combination of phenobarbital and KBr was associated with the largest decrease in activity level between groups. No significant differences in sleep score were detected between groups, but more studies that incorporate the use of EEG and videography to quantify sleep stages are needed.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Approved by the University of Wisconsin—Madison IACUC, protocol # V006156.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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