

## Evaluation of Levetiracetam as Adjunctive Treatment for Refractory Canine Epilepsy: A Randomized, Placebo-Controlled, Crossover Trial

K.R. Muñana, W.B. Thomas, K.D. Inzana, J.A. Nettifee-Osborne, K.J. McLucas, N.J. Olby, C.J. Mariani, and P.J. Early

**Background:** There is little evidence-based information available to guide treatment of refractory epilepsy in dogs. The antiepileptic drug levetiracetam (LEV) is administered to dogs, although its safety and efficacy are unknown.

**Objective:** To evaluate the safety and efficacy of LEV as adjunctive therapy for refractory epilepsy in dogs.

**Animals:** Thirty-four client-owned dogs with idiopathic epilepsy.

**Methods:** Randomized, blinded trial involving dogs resistant to phenobarbital and bromide. Dogs received LEV (20 mg/kg PO q8h) or placebo for 16 weeks, and after a 4-week washout were crossed over to the alternate treatment for 16 weeks. Owners kept records on seizure frequency and adverse events. Hemogram, chemistry profile, urinalysis, and serum antiepileptic drug concentrations were evaluated at established intervals.

**Results:** Twenty-two (65%) dogs completed the study. Weekly seizure frequency during the 1st treatment period decreased significantly during LEV administration relative to baseline ( $1.9 \pm 1.9$  to  $1.1 \pm 1.3$ ,  $P = .015$ ). The reduction in seizures with LEV was not significant when compared to placebo ( $1.1 \pm 1.3$  versus  $1.5 \pm 1.7$ ,  $P = .310$ ). The most common adverse event was ataxia, with no difference in incidence between LEV and placebo (45 versus 18%,  $P = .090$ ). No changes in laboratory parameters were identified and owners reported an improved quality of life (QOL) with LEV compared to placebo (QOL score  $32.7 \pm 4.3$  versus  $29.4 \pm 4.5$ ,  $P = .028$ ).

**Conclusions and Clinical Importance:** Adjunctive treatment with LEV appears safe in epileptic dogs. Efficacy of LEV over placebo was not demonstrated, although the power of the study was limited. Further evaluation of LEV as treatment for epilepsy in dogs is warranted.

**Key words:** Clinical pharmacology; CNS disorders; Dog; Epilepsy; Neurology; Seizures.

Epilepsy is a common neurological disorder in dogs, affecting 0.5–5% of all dogs evaluated at veterinary referral hospitals.<sup>1,2</sup> The mainstay of treatment is antiepileptic drugs, of which phenobarbital and potassium bromide are most commonly prescribed. However, approximately 20–30% of dogs with epilepsy do not have satisfactory seizure control or experience intolerable adverse effects with appropriate conventional medical treatment.<sup>3</sup> Multiple new antiepileptic drugs have been approved for human use over the last 20 years, and several of these are being used in

---

### Abbreviations:

CNS	central nervous system
LEV	levetiracetam
QOL	quality of life
TX1	first treatment period
TX2	second treatment period

---

veterinary medicine in an attempt to better manage dogs with poorly controlled epilepsy.

Levetiracetam (LEV) was approved in 1999 as an adjunct treatment for humans with partial onset seizures. The unique mechanism of action of LEV is advantageous when it is used in combination with other antiepileptic drugs, because differing and complementary mechanisms of action are considered desirable when instituting polytherapy. Furthermore, LEV possesses a favorable pharmacokinetic profile and low adverse effect rate in humans. Based on the success of LEV in the management of epilepsy in humans, there is interest in veterinary medicine regarding its use in epileptic dogs.

Several studies have evaluated the pharmacokinetic properties of LEV in normal dogs when administered by either the oral, intramuscular or intravenous route.<sup>4–7</sup> However, reports of the drug's efficacy in epileptic dogs are limited to 2 open-label studies.<sup>8,9</sup> In addition, a therapeutic range has not been established for dogs. A dose rate of 20 mg/kg every 8 hours has been recommended based on studies in rodent models of epilepsy and pharmacokinetic studies in normal dogs that have determined the dose required to obtain plasma concentrations similar to clinically

---

*From the Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, NC (Muñana, Nettifee-Osborne, Olby, Mariani, Early); the Department of Small Animal Clinical Sciences, College of Veterinary Medicine, University of Tennessee, Knoxville, TN (McLucas, Thomas); and the Department of Small Animal Clinical Sciences, Virginia-Maryland College of Veterinary Medicine, Virginia Tech, Blacksburg, VA (Inzana). This work was performed at the Veterinary Teaching Hospitals of North Carolina State University, Raleigh, NC; the University of Tennessee, Knoxville, TN; and the Virginia-Maryland College of Veterinary Medicine, Blacksburg, VA. Findings from this study were presented at the 2010 American College of Veterinary Internal Medicine Forum, Anaheim, CA.*

*Corresponding author: Karen R. Muñana, North Carolina State University College of Veterinary Medicine, Veterinary Health Complex Room 2569, 1052 William Moore Drive, Raleigh, NC 27607; e-mail: karen\_munana@ncsu.edu.*

*Submitted September 8, 2011; Revised November 7, 2011; Accepted December 2, 2011.*

*Copyright © 2012 by the American College of Veterinary Internal Medicine*

*10.1111/j.1939-1676.2011.00866.x*

relevant plasma concentrations in humans.<sup>4,7</sup> The purpose of this randomized, controlled clinical study was to objectively evaluate the efficacy and safety of LEV as add-on therapy in dogs with poorly controlled epilepsy.

## Materials and Methods

### Study Design

The randomized, placebo-controlled, double-blind, crossover trial was conducted at the veterinary teaching hospitals (VTH) of North Carolina State University (NCSU), University of Tennessee (UT) and Virginia Tech (VT) from 2003 to 2009. Inclusion criteria for the study were (1) onset of seizures between 6 months and 5 years of age, with a minimum documented 6 month history of seizures; (2) average seizure frequency of at least 4 per month or a history of cluster seizures (defined as 3 or more seizures within a 24-hour period); (3) current treatment with antiepileptic drugs at recommended dosages; (4) current or historical treatment with phenobarbital and potassium bromide used concurrently at therapeutic serum concentrations; (5) normal neurological examination; and (6) no abnormalities detected on hemogram, chemistry profile, urinalysis, and bile acid tolerance to suggest an underlying cause for the seizures. Eligible dogs entered an 8-week baseline assessment during which owners recorded daily antiepileptic drugs administered, adverse effects and seizure activity on standard forms designed for the study. Dogs with an average seizure frequency of  $\geq 4$  seizures a month or that experienced cluster seizures during the baseline period were randomized into the study. NCSU-VTH pharmacy personnel performed the study randomization and dispensed all study related medication. Dogs were assigned to an order of treatment groups following simple randomization procedures with a computer-generated list of random numbers. Dogs from the 3 study sites were considered together in the randomization process and were randomized according to enrollment date. Dog owners and veterinary personnel involved in evaluating dogs were kept blinded to the treatment assignment. Dogs underwent two 16-week treatment periods, during which they received oral LEV at a target dosage of 20 mg/kg every 8 hours during 1 period and placebo to match during the second period.<sup>a</sup> LEV was provided in 3 pill strengths (166.5, 250, and 500 mg), and dosage was calculated to the closest half pill. The study included a 4-week wash-out period between the 2 treatment periods, during which the 1st agent administered was titrated down approximately 25% each week. Owners were instructed to continue to collect all data initiated during baseline. Dosages of phenobarbital and potassium bromide were not altered throughout the study. Dogs were evaluated at the following timepoints: initial screening and baseline initiation (week 0), initiation of the 1st treatment period (TX1) (week 8), midpoint of TX1 (week 16), end of TX1 (week 24), initiation of the 2nd treatment period (TX2) (week 28), midpoint of TX2 (week 36) and end of TX2 (weeks 44). At each scheduled visit, the owners' record of seizure activity and adverse effects was reviewed by a blinded investigator. Physical and neurological examination as well as hemogram, serum chemistry profile, urinalysis, and serum concentrations of phenobarbital, bromide, or both were performed at each visit. Blood was collected at weeks 16, 24, 36, and 44 to assay for LEV serum concentrations. Blood samples were centrifuged and serum stored at  $-70^{\circ}\text{C}$  until assayed in batch through a commercial laboratory<sup>b</sup> or the NCSU Clinical Pharmacology Laboratory at the interim analysis or study completion. The study protocol was approved by the Institutional Animal Care and Use Committee at the participating universities. All owners were required to provide informed consent before their dogs' participation in the study.

### Seizure Frequency

Seizure monitoring was based on owner observations, with information recorded on study forms that were adapted from those used for human seizure monitoring. Owners were instructed to complete a daily diary noting dose and time of medication administered, the presence of any seizure activity, and whether any signs of illness, change in activity or attitude were noted. In addition, owners were directed to complete a separate seizure record immediately after any observed seizure to provide a tabulation of number of seizures. Based on the owner records, a weekly seizure frequency was compiled for each dog throughout the study. To standardize the number of seizures for each dog with differing number of weeks of follow up in each of the study periods (ie, 8 weeks for baseline, and 16 weeks for placebo and LEV treatment), the number of seizures reported for each study period were summed up and divided by the number of weeks of observation in that study period. The weekly seizure frequency for each of the study periods (baseline, placebo administration, and active treatment) was calculated and compared as the primary efficacy variable. Secondary efficacy variables compared between treatment periods included the median percent reduction in seizures from baseline, the proportion of dogs classified as responders (experiencing a  $\geq 50\%$  decrease in seizure frequency from baseline), and the proportion of dogs becoming seizure free.

Seizure frequency data from the first 14 dogs to complete the trial were utilized in a study performed by one of the authors on the placebo effect in canine epilepsy trials.<sup>10</sup>

### Quality of Life Questionnaire

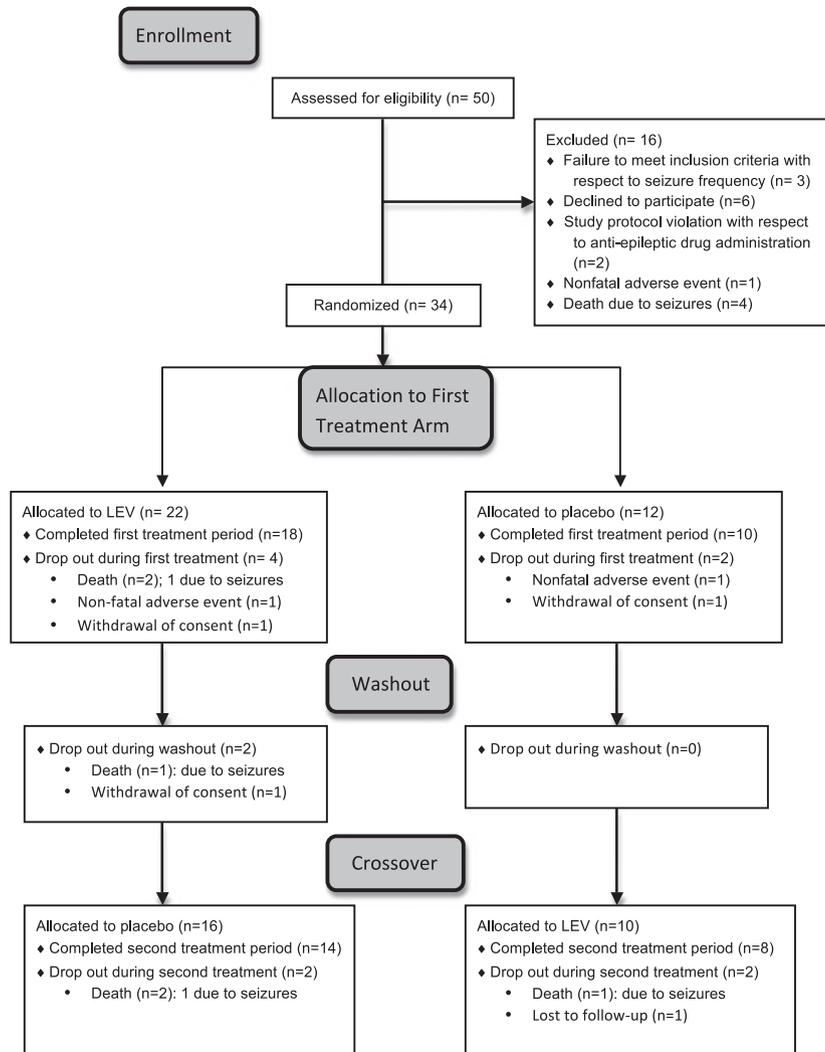
Owners were asked to complete a quality of life (QOL) questionnaire at the end of baseline (week 8) and at the end of TX1 and TX2 (weeks 24 and 44, respectively). The questionnaire was adapted from one previously utilized to assess QOL in epileptic dogs.<sup>11</sup> Owners were asked to answer 12 questions with a bipolar response scale of 1 (strongly agree) to 5 (strongly disagree). Questions were worded such that a better QOL corresponded to a response of 1 in some instances and a response of 5 in others. For the analyses, scales from all the questions were standardized such that a high response to any question was positive. A QOL score was computed by compiling responses to the questionnaire, with a possible score of between 12 and 60, and a higher overall score indicating a better QOL.

### Statistical Analysis

Differences in the distribution of baseline characteristics and secondary efficacy variables between treatment arms were tested with a Fisher's exact test for categorical variables and the Wilcoxon rank sums test for continuous variables. To compare differences between groups at specific time points over the course of the study, mixed models were fit that accounted for the repeated measurements within dogs over time as well as treatment order and week of treatment. For continuous data, mixed linear models were used. For categorical data, generalized estimating equations (GEE) methods were used. A significance level of  $P < .05$  was established for all analyses.

### Results

The disposition of study participants is summarized in Figure 1. Fifty dogs underwent baseline assessment, of which 16 (32%) were subsequently determined to be ineligible and were not randomized. Of the 34 dogs



**Fig 1.** Disposition of dogs participating in the clinical trial.

randomized into the treatment phase of the study, 21 were enrolled through NCSU, 10 were enrolled through UT, and 3 were enrolled through VT. Breeds represented included mixed breed ( $n = 6$ ), Labrador Retriever ( $n = 4$ ), Jack Russell Terrier ( $n = 3$ ), Beagle ( $n = 3$ ), Golden Retriever ( $n = 2$ ), Boxer ( $n = 2$ ), and 1 each of Doberman Pinscher, Pembroke Welsh Corgi, Australian Shepherd, Shih Tzu, Border Collie, Dalmatian, Boykin Spaniel, Collie, Pekingese, Greyhound, Siberian Husky, Pug, Great Dane, and Miniature Poodle. There were 21 males (17 neutered) and 13 spayed females, with a body weight of 25.9 kg (median, range 5.80–75.5 kg). The age at study enrollment was 5.0 years (median, range 1.5–10 years), whereas the age at onset of seizures was 1.5 years (median, range 0.5–5 years). Based on owner description, 24 dogs (71%) had only generalized seizures and 10 dogs (29%) had both generalized and partial motor seizures.

At the time of randomization, 27 dogs (79%) were being administered phenobarbital and bromide, 4 dogs

(12%) were on phenobarbital alone, and the remaining 3 dogs were treated with a combination of bromide and zonisamide ( $n = 1$ , 3%), phenobarbital and gabapentin ( $n = 1$ , 3%), or phenobarbital, bromide and gabapentin ( $n = 1$ , 3%). The daily phenobarbital dose ( $n = 33$ ) was 8.7 mg/kg (median, range 2.9–17.2 mg/kg), with a phenobarbital serum level of 28.13  $\mu\text{g/mL}$  (mean, range 15.77–36.40  $\mu\text{g/mL}$ ). Daily bromide dose ( $n = 29$ ) was 39.1 mg/kg (median, range 13.6–133.3 mg/kg), with a bromide serum concentration of 186.20 mg/dL (mean, range 71.18–390 mg/dL).

Twenty-two dogs were randomized to receive LEV during TX1 and 12 were randomized to receive placebo. The dose of LEV administered was 20.6 mg/kg (median, range 17.0–23.1 mg/kg) every 8 hours. Dog demographics and history of epilepsy with respect to TX1 are summarized in Table 1. Analysis of this data revealed a significant imbalance between initial treatment arms with respect to age of seizure onset ( $P = .027$ ) and bromide dose ( $P = .008$ ). An imbalance was also noted for daily phenobarbital dose, although

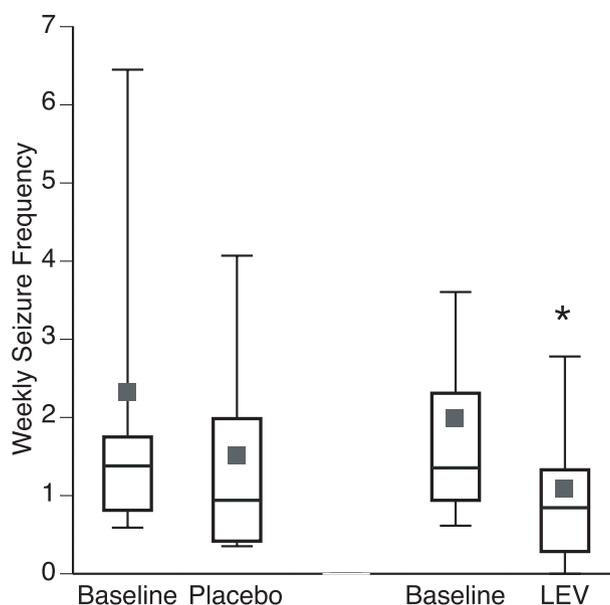
**Table 1.** Patient demographics and history of epilepsy based on 1st treatment period.

Variable	Placebo (n = 12)	Levetiracetam (n = 22)	P-value
Age, years median (range)	5.0 (3.0, 10.0)	4.5 (1.5, 10)	.592
Weight, kg median (range)	27.1 (7.7, 75.5)	24.4 (5.8, 58.0)	.493
Sex			.364
Female spayed	6 (50%)	7 (32%)	
Male	2 (17%)	2 (9%)	
Male neutered	4 (33%)	13 (59%)	
Age at onset of seizures, years median (range)	2.0 (1.0, 4.5)	1.0 (0.5, 5.0)	.027
Seizure duration, years median (range)	2.5 (1.5, 7.0)	3.25 (0.75, 7.0)	.864
Seizure type			1.00
Generalized	9 (75%)	15 (68%)	
Partial and generalized	3 (25%)	7 (32%)	
Phenobarbital dose, mg/kg/d median (range)	9.7 (2.9, 13.8)	7.2 (3.8, 17.2)	.326
Bromide dose, mg/kg/d median (range)	72.2 (22.2, 133.3)	34.0 (13.6, 84.2)	.008

the difference was not significant ( $P = .326$ ). Because differences in antiepileptic drug dosages could bias the outcome measures, the phenobarbital and potassium bromide doses were used as covariates to adjust for these differences. Both unadjusted and adjusted analyses were performed.

Twenty-two dogs (65%) completed the study. Six dogs died during the course of the study, including 4 that died or were euthanized as a result of uncontrolled seizures. One dog died because of acute respiratory distress while being administered placebo and another dog was euthanized because of acute non-ambulatory tetraparesis during LEV administration. Necropsy was not performed in either of these dogs to determine a cause for the clinical signs. There was no difference in dropout rates between the dogs randomized to receive LEV and those randomized to receive placebo during TX1. Dropouts were such that only 16 (73%) of the dogs randomized to LEV for TX1 and 10 (83%) of the dogs randomized to placebo for TX1 crossed over to TX2.

Because the power of the analysis to detect differences among dogs that crossed over to TX2 was reduced by the high dropout rate, subsequent statistical analyses were performed between the group of dogs receiving LEV during TX1 and the group of dogs receiving placebo during TX1, rather than comparing dogs within each group that crossed over to TX2. The weekly seizure frequency during TX1 for LEV and placebo compared to baseline is depicted in Figure 2. There was no significant difference in baseline weekly seizure frequency between the 2 treatment groups in either the unadjusted or adjusted analysis ( $P = .774$  and  $P = .640$ , respectively). Dogs receiving LEV during TX1 has a significant decrease in weekly seizure frequency compared to baseline ( $1.9 \pm 1.9$  to  $1.1 \pm 1.3$  (mean, SD),  $P = .015$ ). Dogs receiving placebo during TX1 had a weekly seizure frequency of  $1.5 \pm 1.7$  compared to  $2.2 \pm 3.3$  at baseline ( $P = .098$ ). When the weekly seizure frequency during TX1 was compared between dogs receiving LEV and dogs receiving placebo, no significant difference was identified in either the unadjusted or adjusted analysis ( $P = .497$  and  $P = .310$ , respectively).



**Fig 2.** Mean weekly seizure frequency relative to baseline for dogs receiving placebo (n = 12) and levetiracetam (n = 22) during the 1st treatment period. Central lines of the box represent the median, upper and lower limits of the box represent the 75th and 25th percentiles, and whiskers represent the 90th and 10th percentiles. Mean values are denoted by ■. \* denotes a statistically significant difference compared to baseline.

Secondary efficacy variables were evaluated for the 28 dogs completing TX1. No significant difference was identified between dogs receiving LEV and dogs receiving placebo with respect to percent reduction in seizures compared to baseline (median, 61 versus 39%,  $P = .116$ ), proportion of dogs classified as responders with a  $\geq 50\%$  decrease in seizure frequency from baseline (56 versus 30%,  $P = .184$ ), or proportion of dogs becoming seizure free (17 versus 0%,  $P = .249$ ).

For the group of dogs as a whole, there was a statistically significant decrease in weekly seizure frequency over the course of the study ( $P = .015$ ) regardless of treatment order. Weekly seizure frequency during baseline, TX1, and TX2 was  $2.1 \pm 2.5$ ,  $1.2 \pm 1.5$ , and  $1.0 \pm 1.0$ , respectively.

The most frequent adverse events reported throughout the study were ataxia, restlessness, anorexia, and vomiting (Table 2). Ataxia denoted owner-based observations of clumsiness, stumbling, wobbly or drunken gait, incoordination, or poor balance. A significant increase in the incidence of any adverse event ( $P = .013$ ) and ataxia in particular ( $P = .002$ ) was noted in dogs receiving LEV during TX1 compared to baseline. Although adverse events were reported more often in dogs receiving LEV during TX1, analysis did not demonstrate a significant difference in incidence compared to placebo ( $P = .186$ ). No clinically relevant change from baseline was found for any laboratory parameter on hemogram, chemistry profile or urinalysis, and no differences in mean serum phenobarbital and bromide concentrations were identified during LEV administration compared to placebo.

Levetiracetam serum concentrations were measured in 26 dogs at 8 and 16 weeks after initiation of LEV treatment. The timing of sample collection was not standardized for the study. Serum LEV concentrations were highly variable, ranging from  $<2$  to  $50.8 \mu\text{g/mL}$ . Values less than  $5 \mu\text{g/mL}$  were obtained at one or more sampling points in 10 (38%) of the dogs. Linear regression analysis did not identify an association between LEV serum concentration and weekly seizure frequency ( $r^2 = 0.09$ ,  $P = .25$ ). Similarly, the serum LEV concentrations did not differ significantly between dogs classified as responders and nonresponders (Fig 3).

In evaluation of QOL scores, both unadjusted and adjusted comparisons were computed. There was no significant difference in baseline QOL scores between dogs receiving LEV during TX1 and those receiving placebo. The QOL score increased from a baseline value of  $30.4 \pm 5.6$  to  $32.7 \pm 4.3$  (mean, SD) during administration of LEV in TX1 ( $P = .009$ ). The dogs receiving placebo during TX1 had an increase in QOL score from baseline of  $28.5 \pm 5.1$  to  $29.4 \pm 4.5$  ( $P = .591$ ). As the QOL score was lower in the placebo group at baseline, an additional model was fit to adjust for this. The resulting covariate analysis revealed a significant difference between LEV and placebo groups at TX1 ( $P = .028$ ). In addition, a significant increase in QOL score was noted for all dogs over the course of the study, regardless of treatment

**Table 2.** Adverse events reported throughout the study based on treatment group (incidence 5% or more in at least one treatment group).

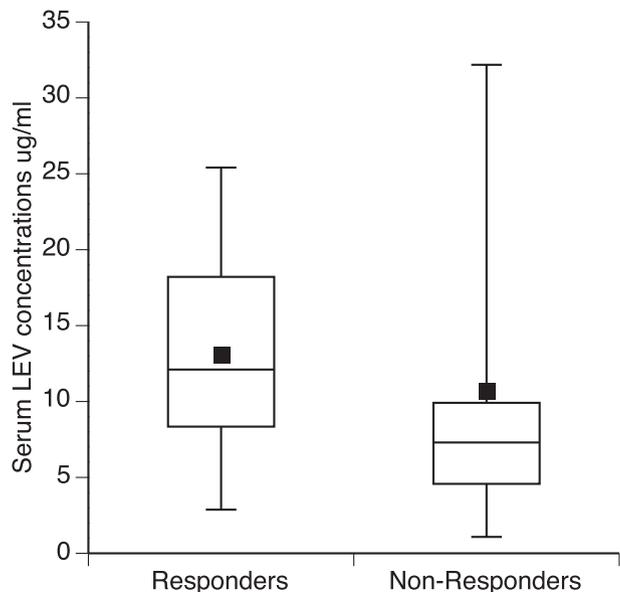
Adverse Event	Baseline (n = 34)	Placebo (n = 26)	Levetiracetam (n = 28)
Any adverse event	14 (41%)	11 (43%)	16 (57%)
Ataxia	7 (21%)	6 (23%)	11 (39%)
Restlessness	4 (12%)	3 (12%)	4 (14%)
Vomiting	1 (3%)	2 (8%)	3 (11%)
Decreased appetite	1 (3%)	1 (4%)	2 (7%)

group ( $29.7 \pm 5.4$  during baseline,  $31.5 \pm 4.6$  during TX1,  $32.5 \pm 3.8$  during TX2,  $P = .0002$ ). Owners of 9 (41%) of the dogs completing the study chose to continue to utilize LEV as a component of their dog's long-term epilepsy treatment regimen.

## Discussion

The aim of the present study was to objectively evaluate LEV as a treatment for medically resistant canine epilepsy. Results of this study failed to demonstrate the efficacy of LEV compared to placebo when administered as add-on therapy in dogs with refractory epilepsy. Although LEV appeared to be efficacious relative to baseline, no significant difference was identified when seizure frequency during LEV administration was compared to placebo.

Currently, there is no evidence-based consensus in veterinary medicine regarding the optimal approach to managing a dog with refractory epilepsy. Rather, treatment recommendations are frequently based on clinical experience and results of a few open label trials. Two previously published open-label trials on LEV as add-on therapy for refractory epilepsy in dogs have reported a favorable treatment response compared to baseline.<sup>8,9</sup> In 1 study involving 14 dogs, a 77% decrease in seizure frequency was reported during LEV administration compared to baseline, and 57% of dogs were classified as responders.<sup>8</sup> An overall reduction in seizure frequency of 54% compared to baseline with LEV administration was reported in a 2nd study of 15 dogs.<sup>9</sup> Findings from these open-label trials suggest



**Fig 3.** Mean serum levetiracetam (LEV) concentrations in dogs classified as responders ( $\geq 50\%$  reduction in seizures during LEV administration compared to placebo) and nonresponders. Central lines of the box represent the median, upper and lower limits of the box represent the 75th and 25th percentiles, and whiskers represent the 90th and 10th percentiles. Mean values are denoted by ■.

that LEV administration is effective in controlling seizures in refractory epilepsy in dogs, which is not in accordance with the results of the present placebo controlled trial. Open-label observational studies of epilepsy treatments in humans frequently identify greater efficacy compared to randomized controlled trials,<sup>12</sup> and has been demonstrated with LEV.<sup>13</sup> This has been attributed to potential selection bias in the case of open-label trials, as well as the potential loss of investigator and patient objectivity in such studies.<sup>12,13</sup>

Furthermore, the previous studies evaluating LEV for epilepsy in dogs were not designed to account for any placebo response, and consequently the reported efficacy in these studies is likely overstated based on the surprisingly large placebo effect demonstrated in the present study. The first 14 dogs to complete the current trial were included in a recently published report on the placebo effect in dogs with epilepsy.<sup>10</sup> The study involved dogs from 2 other randomized epilepsy trials, and identified an overall placebo response rate of 29%.<sup>10</sup> A clinical benefit attributable to placebo administration is commonly identified in controlled trials involving humans with epilepsy. Meta-analyses of randomized add-on trials of antiepileptic drugs have demonstrated a pooled placebo responder rate of 10–15%,<sup>14–16</sup> with a statistically significant placebo effect identified in 20 of 27 studies in 1 analysis.<sup>16</sup> In addition, a recent review of the efficacy of newer anti-epileptic drugs relative to placebo demonstrated relatively small placebo-corrected responder rates of 6–21% for these drugs.<sup>17</sup> The placebo response observed in epilepsy trials has been attributed to regression to the mean, or the natural tendency for seizures to wax and wane over the course of disease, and for novel treatment to be initiated when seizures are most severe, such that seizures should improve over time regardless of treatment. Other factors that might play a role are the Hawthorne effect, in which individuals report an improvement that is attributed to additional attention provided during study participation, and the potential for improved adherence to the anti-epileptic drug treatment regimen during study participation. Interestingly, dogs in the present study demonstrated a significant reduction in seizure frequency over the course of the study as well as a significant improvement in owner perceived QOL, regardless of treatment arm. This supports the notion that factors independent of the medication being administered are contributing to the improvement noted.

Levetiracetam is promoted as having a wide margin of safety when compared to other antiepileptic drugs. Findings from this study support the premise that LEV is generally well tolerated when used as add-on therapy in dogs with epilepsy, but it is not free of adverse effects when administered at a dose of 20 mg/kg every 8 hours. A significant increase in ataxia was identified during LEV administration compared to baseline, but was not determined to be significant when compared to placebo. However, the difference in incidence of ataxia between the dogs that received LEV and those that received placebo during TX1 (45

versus 18%,  $P = .090$ ) was fairly large, and it is possible that significance would have been achieved with a larger sample population. The only previously reported adverse event attributed to LEV was transient sedation in 1 dog.<sup>8</sup> LEV treatment was initiated at a lower dose (10 mg/kg every 8 hours) than that utilized in the current study, and as it is common for central nervous system (CNS)-related adverse events such as ataxia to increase with higher doses of antiepileptic drugs,<sup>18</sup> the difference in findings between the 2 studies might be explained by this. The most common adverse events associated with LEV administration in humans are also CNS related, and include asthenia, somnolence, and headache.<sup>19,20</sup> Vomiting and decreased appetite were reported in dogs in the present study, and nausea has been described as an uncommon adverse event in humans.<sup>19</sup> In addition, LEV administration has demonstrated no clinically relevant effect on routine laboratory parameters<sup>21</sup> or on serum antiepileptic drug concentrations in humans,<sup>22</sup> and findings from the present trial suggest this might be the same in dogs.

A significant improvement in QOL score was identified during LEV administration compared to placebo. A reduction in seizure frequency was also observed during LEV administration compared to placebo, which was not statistically significant but nonetheless might have resulted in modest changes that owners perceived as improved QOL in their dogs. It is also possible that LEV administration somehow improved QOL independent of seizure control, but this is considered less likely. The improved QOL cannot be attributed to a decrease in medication-related adverse effects, as the incidence of adverse events increased during LEV administration. Furthermore, there were no adjustments to dosages of other antiepileptic drugs during the study that could have accounted for an improved QOL by alleviating a less tolerable adverse effect associated with another medication.

Considerable variability in LEV serum concentrations was identified among study dogs, and wide fluctuations in LEV serum concentrations were noted in individual dogs across sampling points. This variability might be caused by the lack of standardization in the timing of sample collection with respect to drug administration. LEV has a half-life of approximately 3 hours in dogs,<sup>5,7</sup> and consequently, variations in serum concentrations are expected during an 8-hour dosing interval. Appointment times varied among the participating study centers, and the long distance that some owners traveled to participate in the study limited the time of day that dogs were evaluated. The wide range of LEV concentrations identified in this study might also be a reflection of interindividual variation, which has been reported in humans.<sup>23</sup> Ideally, both peak and trough serum concentrations would have been evaluated in each dog, although this was not possible within the constraints of this study.

A therapeutic range for LEV has not been established in humans. Target ranges suggested for seizure control have been reported as 12–46,<sup>24</sup> 13–42,<sup>25</sup> and 5–30 µg/mL,<sup>26</sup> although routine monitoring of LEV

concentrations is rarely performed in clinical practice. There is no information available regarding a therapeutic range in dogs. However, if one utilizes the human reference range and assumes a minimum serum concentration of 5 µg/mL is needed to achieve seizure control in dogs, it is interesting to note that 38% of dogs in the present study had concentrations at one or more sampling point that would be considered subtherapeutic. All of the dogs were concurrently being administered other antiepileptic drugs, with phenobarbital prescribed most commonly. Studies in humans have shown that concomitant administration of antiepileptic drugs that induce cytochrome P450 metabolism, such as carbamazepine, phenobarbital, and phenytoin, can alter the disposition of LEV.<sup>27</sup> Recently, it has been demonstrated that phenobarbital administration significantly alters the pharmacokinetics of LEV in normal dogs.<sup>28</sup> These findings suggest that the standard recommended dosage of 20 mg/kg every 8 hours might not be sufficient to maintain serum concentrations within the proposed therapeutic range when LEV is used in conjunction with phenobarbital.

An association between LEV serum concentrations and response to treatment was not identified in the dogs studied. Similarly, no straightforward relationship has been identified between LEV concentrations and clinical effects in humans.<sup>23</sup> Further study is necessary to establish a therapeutic range in dogs, as well as to determine recommendations for therapeutic monitoring in dogs when LEV is administered to dogs concurrent with other antiepileptic drugs.

One major weakness of the study is the divergence in group sizes for the 1st treatment period that occurred despite randomization; 22 dogs were randomized to receive LEV during the 1st treatment period, whereas only 12 dogs were randomized to receive placebo. This is attributed to the simple randomization process used, which was judged to be adequate during study design based on the crossover nature of the trial. However, the unanticipated high dropout rate resulted in a disparity in the size of groups available for data analysis at study completion. This problem could have been avoided by utilizing block randomization, reviewing the randomization scheme produced by the random number generator to ensure that balance was achieved, or performing an interim analysis and changing the allocation of dogs to study groups as needed.

Additional limitations in this study are a reflection of the relatively small sample size. The high dropout rate resulted in a lower number of dogs completing the study than anticipated, and negatively influenced the power of the study to detect a difference in treatment groups. The power analysis performed as part of the trial design established a target enrollment of 50 dogs, and accounted for a 10% dropout rate. The actual dropout rate for dogs randomized into the study was 35%, and is believed to be a manifestation of the severity of epilepsy in the population of dogs studied. As LEV was evaluated as add-on therapy for refractory epilepsy, the study selected for dogs with severe, poorly controlled seizures. Of the 50 dogs enrolled in

the study, 8 (16%) died or were euthanized during the course of the study as a direct result of the severity of their seizures. A 2nd factor that weakened the power of the study to detect a difference in treatment arms was the magnitude of the placebo effect. Indeed, knowledge of the magnitude of the placebo effect is very important in calculating sample size in the planning of placebo-controlled clinical trials,<sup>16</sup> and limited information was available in this regard at the time of trial initiation. Finally, epidemiological studies in humans with epilepsy have documented that only a small number of individuals who are refractory to 2 or more antiepileptic drugs achieve better seizure control when a 3rd medication is added to the treatment regime,<sup>29</sup> and it is possible that a similar situation exists in dogs. Consequently, a larger sample population might be required to identify a beneficial effect of LEV administration. The trend toward a decrease in seizure frequency and increase in responder rate during LEV administration compared to placebo that was identified in this trial warrants further evaluation in a larger scale study.

Results of the study suggest that LEV is safe when used as adjunctive treatment in dogs with poorly controlled epilepsy and that owners perceive an improved QOL for their dog during LEV administration, although the study failed to establish the efficacy of LEV when compared to placebo. The study also identified some obstacles inherent in epilepsy trials in dogs, including case dropout and the placebo effect. Knowledge of these should prove valuable in the design of future epilepsy trials in dogs. Additional studies are needed to better understand the potential role of LEV in the treatment of epilepsy in dogs both as add-on therapy and as a first-line treatment.

---

## Footnotes

<sup>a</sup> UCB Pharma, Smyrna, GA

<sup>b</sup> MedTox Laboratories, St. Paul, MN

---

## Acknowledgments

The authors thank Jeff Johnson for his assistance with the statistical analyses, and acknowledge the referring veterinarians and owners of dogs that participated in the study.

This study was supported by Morris Animal Foundation and UCB Pharma Inc.

## References

1. Cunningham JG, Farnbach GC. Inheritance and idiopathic canine epilepsy. *J Am Anim Hosp Assoc* 1988;24:421-424.
2. Oliver JE. Seizure disorders in companion animals. *Comp Cont Ed Pract Vet* 1980;2:77-85.
3. Lane SB, Bunch SE. Medical management of recurrent seizures in dogs and cats. *J Vet Intern Med* 1990;4:26-39.

4. Isoherranen N, Yagen B, Soback S, et al. Pharmacokinetics of levetiracetam and its enantiomer (R)- $\alpha$ -ethyl-2-oxo-pyrrolidine acetamide in dogs. *Epilepsia* 2001;42:825–830.
5. Patterson EE, Goel V, Cloyd JC, et al. Intramuscular, intravenous and oral levetiracetam in dogs: Safety and pharmacokinetics. *J Vet Pharmacol Ther* 2008;31:253–258.
6. Dewey CW, Bailey KS, Boothe DM, et al. Pharmacokinetics of single-dose intravenous levetiracetam administration in normal dogs. *J Vet Emerg Crit Care* 2008;18:153–157.
7. Moore SA, Muñana KR, Papich MG, Nettifee-Osborne J. Levetiracetam pharmacokinetics in healthy dogs following oral administration of single and multiple doses. *Am J Vet Res* 2010;71:337–341.
8. Volk HA, Matiasek LA, Luján Feliu-Pascual A, et al. The efficacy and tolerability of levetiracetam in pharmacoresistant epileptic dogs. *Vet J* 2008;176:310–319.
9. Steinberg M, Faissler D. Levetiracetam therapy for long-term idiopathic epileptic dogs. *ACVIM Abstracts. J Vet Intern Med* 2004;18:410.
10. Muñana KR, Zhang D, Patterson EE. Placebo effect in canine epilepsy trials. *J Vet Intern Med* 2010;24:166–170.
11. Lord LK, Podell M. Owner perception of the care of long-term phenobarbital-treated epileptic dogs. *J Small Anim Pract* 1999;40:11–15.
12. Maguire MJ, Hemming K, Hutton JL, Marson AG. Overwhelming heterogeneity in systematic reviews of observational anti-epileptic studies. *Epilepsy Res* 2008;80:201–212.
13. Morrell MJ, Leppik I, French J, et al. The KEEPER™ trial: Levetiracetam adjunctive treatment of partial-onset seizures in an open-label community-based study. *Epilepsy Res* 2003;54:153–161.
14. Burneo JG, Montori VM, Faught E. Magnitude of the placebo effect in randomized trials of antiepileptic agents. *Epilepsy Behav* 2002;3:532–534.
15. Cramer JA, Fisher R, Ben-Menachem E, et al. New antiepileptic drugs: Comparison of key clinical trials. *Epilepsia* 1999;40:590–600.
16. Guekht AB, Korczyn AD, Bondareva IB, Gusev EI. Placebo responses in randomized trials of antiepileptic drugs. *Epilepsy Behav* 2010;17:64–69.
17. Beyenburg S, Stavem K, Schmidt D. Placebo-corrected efficacy of modern antiepileptic drugs for refractory epilepsy: Systematic review and meta-analysis. *Epilepsia* 2010;51:7–26.
18. Zaccara G, Gangemi PF, Cincotta M. Central nervous system adverse effects of new antiepileptic drugs. A meta-analysis of placebo-controlled studies. *Seizure* 2008;17:405–421.
19. Betts T, Waegemans T, Crawford P. A multicentre, double-blind, randomized, parallel group study to evaluate the tolerability and efficacy of two oral doses of levetiracetam, 2000 mg daily and 4000 mg daily, without titration in patients with refractory epilepsy. *Seizure* 2000;9:80–87.
20. Shovron SD, Löwenthal A, Janz D, et al. Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in patients with refractory partial seizures. *European Levetiracetam Study Group. Epilepsia* 2000;41:1179–1186.
21. French J, Edrich P, Cramer JA. A systematic review of the safety profile of levetiracetam; a new antiepileptic drug. *Epilepsy Res* 2001;47:77–90.
22. Gidal BE, Baltès E, Otoul C, Perucca E. Effect of levetiracetam on the pharmacokinetics of adjunctive antiepileptic drugs: A pooled analysis of data from randomized clinical trials. *Epilepsy Res* 2005;64:1–11.
23. Lancelin F, Franchon E, Kraoul L, et al. Therapeutic drug monitoring of levetiracetam by high-performance liquid chromatography with photodiode array ultraviolet detection: Preliminary observations on correlation between plasma concentration and clinical response in patients with refractory epilepsy. *Ther Drug Monit* 2007;29:576–583.
24. Leppik IE, Rarick JO, Walezak TS, et al. Effective levetiracetam doses and serum concentrations: Age effects. *Epilepsia* 2002;43(Suppl 7):240.
25. Folland C, Moriarty GL. Clinical experience of levetiracetam (LEV) in refractory adult epilepsy patients. *Epilepsia* 2002;43(Suppl 7):192.
26. Juenke JM, Brown PI, Urry FM. Analysis of levetiracetam and zonisamide in plasma and serum by HPLC. *Clin Chem* 2002;48(Suppl 6):44–45.
27. Contin M, Albani F, Riva R, Baruzzi A. Levetiracetam therapeutic monitoring in patients with epilepsy: Effect of concomitant antiepileptic drugs. *Ther Drug Monit* 2004;26:375–379.
28. Moore SA, Muñana KR, Papich MG, Nettifee-Osborne JA. The pharmacokinetics of levetiracetam in healthy dogs concurrently receiving phenobarbital. *J Vet Pharmacol Ther* 2011;34:31–34.
29. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000;342:314–319.