PEER REVIEWED

THE CANINE SEIZURE PATIENT
Four Important Questions

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Epilepsy is a common canine disease—thought to affect up to 1 in 20 dogs—and potentially life threatening.[1] A useful working understanding is essential for the small animal practitioner.

When a patient presents for an episode of odd behavior or movement, the clinician must immediately consider 4 questions:

1. Are the events described by the owner (or recorded on video) truly a seizure?
2. Can an underlying cause be identified and treated versus treating only the seizure?
3. Should an anti-epileptic drug (AED) be administered?
4. If medical therapy is pursued, which AED should be chosen?

1 IS THE EVENT A SEIZURE?

There are many behaviors, events, and diseases that mimic a true seizure (**Table 1**).

Electroencephalography

Electroencephalography (EEG) records the brain's electrical activity and is considered by many human physicians to be an essential tool for characterizing seizure

TABLE 1. Behaviors, Events, & Diseases with Seizure-Like Appearance

- Atlantoaxial subluxation
- Breed and drug induced dyskinesia/movement disorders
- Cataplexy, narcolepsy, rapid eye movement (REM) sleep disorder
- Cervical muscle spasm
- Chiari malformation/syringomyelia associated episodes
- Encephalitis
- Episodes of neuromuscular disease
- Exercise-induced collapse
- Extreme agitation
- Head bobbing/tremor syndromes
- Intermittent decerebrate/decerebellate rigidity
- Jaw chomping/fly biting
- Metabolic/toxic event
- Myoclonus
- Syncope
- Vestibular episode

PROFILE OF EPILEPSY

Definition

Epilepsy is defined as *2 or more seizures, at least 24 hours apart, resulting from a nontoxic, nonmetabolic cause.*

An **epileptic seizure** is defined as *a transient occurrence of signs, symptoms, or both due to abnormal, excessive, or synchronous neuronal activity in the brain.*[2] Seizure events can result from:

- Disease localized to the brain (symptomatic/structural)
- A reaction of the healthy brain to a metabolic or toxic insult (reactive)
- An unknown or genetic cause (idiopathic).

In human medicine, the term *idiopathic* has been replaced by the terms *genetic* or *seizure of unknown cause*.[2]

Classification by Frequency

Seizures can be classified into 3 categories based on frequency.[3]

1. **Cluster**: 2 or more seizures within 24 hours
2. **Acute repetitive**: 2 or more seizures within 5 to 12 hours, separate from normal seizure pattern
3. **Status epilepticus**: Continuous seizure for 5 or more minutes ***or*** 2 or more seizures with no recovery between seizures

Classification by Breed

In veterinary medicine, epilepsy is considered genetic when the frequency in a breed exceeds that of the general population (eg, Petit Basset Griffon Vendeen).[4] Classifying seizures by breed is important—certain types of genetic epilepsy have different prognoses, and much interest exists with regard to using dogs as models for human epilepsy.

Border collies have a 2-year median survival from time of seizure onset, with 94% affected by cluster seizures, 53% status epilepticus, and 71% rate of drug resistance.[5] Conversely, the Lagotto Romagnolo has seizure onset at 5 weeks, which spontaneously resolves by 13 weeks, similar to benign familial neonatal seizure in humans.[6]

events (**Figures 1–3**). However, EEG is not a readily available clinical tool in veterinary medicine, and a first-time EEG recorded between seizures in an epileptic human or dog has about a 25% chance of identifying the event as a seizure.[7]

Observation

Identification of a seizure is most often achieved by comparing the observed event to what is considered a typical seizure.

- **Generalized tonic clonic seizures** typically last 1 to 2 minutes, and characteristically feature loss of consciousness, muscle tone and movement (tonic/clonic), jaw chomping, and profuse salivation, followed by gradual return to consciousness and normal ambulation.
- **Partial or nonconvulsive seizures** are more difficult to recognize, with the latter requiring an EEG recording during the event.[8]

In human medicine, classifying events by description alone (without EEG) is accurate, but also allows overdiagnosis of nonepileptic events as seizures. Therefore, observation has high sensitivity, low specificity, and low positive predictive value.[9] Accordingly, clinicians should be aware that they may be treating nonepileptic events with an AED.[10]

2 DOES THE SEIZURE HAVE AN UNDERLYING CAUSE?

Identifying an underlying cause for the seizure yields better seizure control, quality of life, and accurate prognosis. The most recent seizure classification system—by cause—groups seizures into 3 causes: genetic, structural/metabolic, and unknown.

Genetic & Unknown Causes

Diagnosis of **idiopathic epilepsy** (IE) is made when:

- Genetic basis is suspected
- Testing has failed to reveal a cause for the seizure.

Structural/Metabolic Causes

- Diagnosis of structural epilepsy is often made by magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis, with common causes, including brain tumor, infarct or hemorrhage, or encephalitis.
- Technically, most metabolic causes of seizure are not a form of epilepsy because the brain itself is normal and reacting to an extracranial insult, which once eliminated, results in cessation of seizure.

Because MRI and CSF analysis are expensive and not readily available, the primary care clinician is often faced with making a difficult decision about whether to refer a patient or simply prescribe an AED. Key factors in assessing a seizure patient include:

Age

As a guideline, dogs with IE typically have their first seizure between 6 months and 6 years of age. However, at seizure onset, about 20% of dogs older than 6 years, and 2% of dogs younger than 6 months, do not have an identifiable cause for seizure.[11]

Breed

There are, however, some exceptions to the age rule noted above. Seizure is a very common presenting complaint in

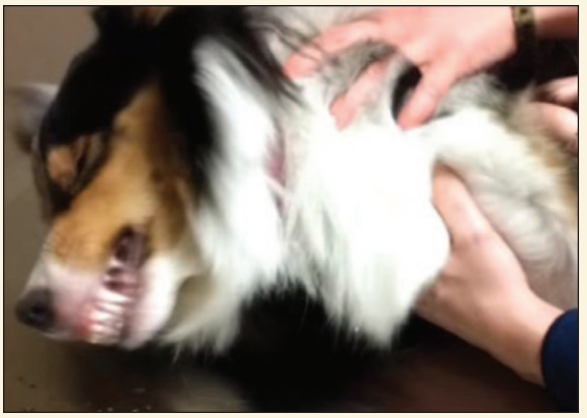

Figure 1. *A 3-year-old collie mix was presented for cluster seizure; this image shows the patient during a generalized tonic clonic seizure. Another seizure was recorded by EEG and on video (see page 35).*

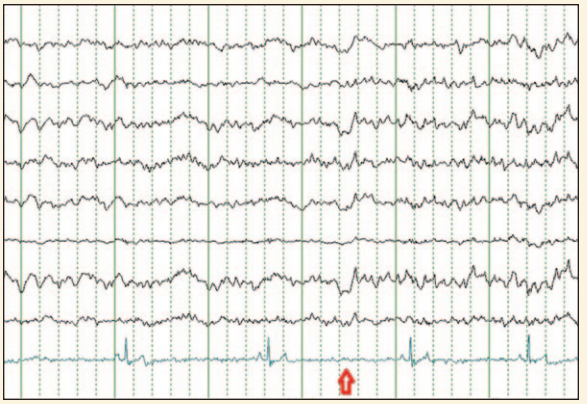

Figure 2. *EEG recorded under dexmedetomidine sedation in a double banana montage with electrocardiography; the patient was not demonstrating a clinical seizure at this point in the EEG. The red arrow indicates first appearance of generalized sharp waves most prominent in the frontal parietal area, which indicates the presence of electrical activity consistent with a seizure, even though the patient was not actively seizuring at the time.*

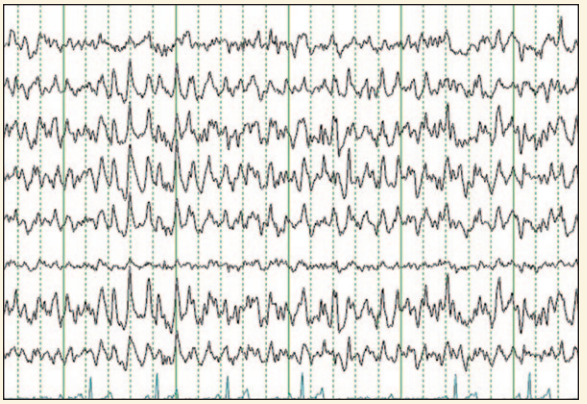

Figure 3. *EEG recorded while the patient is experiencing an electrical and clinical generalized tonic clonic seizure, demonstrating more frequent and higher amplitude generalized sharp waves.*

dogs with brain tumors such that, in certain breeds (eg, golden retriever, boxer, Boston terrier, French bulldog), even 1 seizure at 4 years or older should be cause for concern.[12] In young (1–5 years of age), small breed dogs (eg, pug, Chihuahua, Maltese, poodle) that have 3 or more seizures within a few months, meningoencephalitis of unknown etiology (MUE) should be considered a likely cause for the seizures.

Behavior

Even subtle behavior changes around the time of the first seizure indicate that a patient is likely to have symptomatic epilepsy (**Table 2**).

TABLE 2. Common Behavior Changes in Dogs with Structural Brain Disease

- Aggression
- Inappropriate elimination
- Irritability
- Lethargy/head pressing
- Not greeting owners
- Restless at night
- Sleeping more during the day

Examination Findings

If a neurologic examination performed between seizures has abnormal results, there is a high probability that a structural brain lesion is the cause of the seizure. However, 30% of brain tumor patients will have a normal examination, and 18% of idiopathic epileptics can have a transiently abnormal examination.[10]

It is useful to observe a seizure patient in the examination room to evaluate gait and behavior, coupled with an examination of the postural reactions and menace response. As a guideline, the following findings suggest structural disease, although other causes are possible:

- Confusion
- Circling to one side
- Postural reaction
- Menace deficits on one side.

3 SHOULD AN AED BE ADMINISTERED?

AED drug therapy is recommended if any of the following are present/occur:

- Structural cause for the seizure
- Severe first seizure or post-ictal period
- Owner preference to reduce chances of another seizure.

Read **The Neurologic Examination in Companion Animals—Part 1: The Examination** (January/February 2013) and **Part 2: Interpreting Findings** (March/April 2013)—at **tvpjournal.com** (enter "neurology" in the search bar in the upper right-hand corner of the homepage).

For IE, I recommend AED therapy after 1 or 2 seizures in a 6- to 12-month period for several reasons:

1. Although rarely life-threatening, seizures are very upsetting to owners, and a recent owner survey showed that most owners felt the only acceptable seizure control is no seizure.[13]
2. AED therapy likely reduces the chance of a life-threatening seizure/status epilepticus.
3. Although controversial, there is both bench-top and clinical data that demonstrates every seizure a patient experiences increases the chance for another seizure, independent of the seizure cause. In other words, seizure begets seizure.[14,15]
4. Newer generation AEDs do not have as many side effects or organ toxicities compared to older AEDs, and are now available in generic or cost-effective formulations (**Table 3**, page 34).[16-18]

4 WHICH AED SHOULD BE CHOSEN FOR THERAPY? Maintenance Therapy

When and which AED to apply in the clinical setting remains uncertain and controversial (see **Studies Evaluating AED Efficacy & Safety**). Some reasonable guidelines for seizure management are to:

- Use one medication at a time
- Choose medications with best efficacy, lowest cost/dosing interval, fewest side effects, and lowest risk of toxicity.

Table 3 lists AEDs in the order they are used by most neurologists in our clinic.[11,19]

When to Change. Side effects or lack of efficacy can prompt the need to change AEDs. Studies show that only about 70% of dogs are well controlled on an AED,[17] and fewer than half the dogs on phenobarbital and/or bromide are seizure-free without adverse medication-related side effects.[20]

Treating with multiple AEDs may be beneficial because

Studies Evaluating AED Efficacy & Safety

In veterinary medicine, placebo-controlled or crossover studies to determine the effectiveness or side effects of a sole AED (monotherapy) are lacking.

Multiple studies have evaluated the addition of a newer generation AED (ie, pregabalin, levetiracetam, zonisamide) to phenobarbital ± bromide therapy, resulting in at least a 50% reduction in seizure frequency.[21-23] However, placebo has been shown to reduce the number of seizures in dogs 79% of the time, and also reduces seizure frequency by 50% in 29% of patients.[24] One explanation for the placebo effect is *regression to the mean*—a term used to describe fluctuations in biological variables that occur over time, and take the form of a sine wave around the mean.[24]

When levetiracetam was evaluated as an add-on in a placebo-controlled, randomized, crossover study, a significant reduction in seizure frequency was not observed; however, quality of life was considered better on levetiracetam relative to placebo.[25]

they act on a broader range of mechanisms or synergistically; however, side effects can be additive, and determining which AED is effective is difficult when more than one medication is administered. Generally, I recommend using one AED at a time; therefore, AEDs often need to be switched rather than added.

Transition Period. Abrupt cessation or missed doses of AEDs is a common cause of seizure and status epilepticus in humans. This may be of less concern in dogs—only 6% of status epilepticus cases in one study resulted from low AED concentration.[26] Nevertheless, tapering the dose prior to stopping an AED is recommended. Risk of seizure can be further reduced if at least one AED is maintained in the therapeutic range during the transition. **See Step-by-Step: Transitioning to Newer Generation AEDs**.

Rescue Therapy

AED therapy—additional or different, oral or parenteral—to control cluster seizures or status epilepticus is called *rescue therapy*. Rescue plans for epilepsy patients are recommended because, among dogs being treated for IE, a 59% incidence of status epilepticus and higher rates of cluster seizures have been described.[27] Furthermore, a 25% mortality rate among all dogs that present for status epilepticus has been reported.[26]

Predicting Seizures. Recent EEG evidence suggests seizures in dogs are not random events, and that forecasting seizures is possible.[28] Therefore, while therapy can be initiated after a seizure, it can potentially be administered before a seizure, as many owners feel they can predict when seizures will occur.

Oral Therapy. Oral rescue therapy is appropriate if time to next seizure is an hour or greater, allowing for gastrointestinal absorption and development of useful serum concentration. For example, levetiracetam takes about 81 minutes to reach maximal serum concentration following oral administration.[29]

STEP-BY-STEP: TRANSITIONING TO NEWER GENERATION AEDS

1. **For 1 week**, add a new AED to the patient's current regimen.
2. **For the next 5 days**, reduce the dose of the former AED by 50%.
3. **For the next 5 days**, reduce the frequency of the former AED to once a day.
4. **Discontinue** administration of the former AED.

- If **marked sedation, ataxia, or weakness** are noted with the new AED, more rapid tapering or discontinuation of the former AED is advised.
- If **marked increase in seizure frequency** is noted in the following weeks to months, a return to the former AED or addition/substitution of a new, different AED is recommended.

TABLE 3. AED Maintenance Therapy in Dogs
(Side Effect Scale: 1 = Relatively Mild; 5 = Relatively Severe)

DRUG	DOSE	SIDE EFFECT SCALE	PRIMARY SIDE EFFECTS	REPORTED TOXICITY/DYSFUNCTION
Levetiracetam*	**20–50 mg/kg** PO Q 8 H (***or*** Q 12 H for extended release)	1	Ataxia, sedation	None
Zonisamide*	**5–10 mg/kg** PO Q 12 H	2	Ataxia, decreased eating, sedation	Affects liver and kidneys Causes urinary calculi
Gabapentin	**10–30 mg/kg** PO Q 8 H	2	Sedation	None
Pregabalin	**2–4 mg/kg** PO Q 12 H	2	Sedation	None
Phenobarbital*	**2–6 mg/kg** PO Q 12 H	4	Ataxia, polydipsia, polyphagia, polyuria, sedation, weakness	Affects liver, bone marrow, skin, and endocrine system
Bromide*	**25–50 mg/kg** PO Q 8 H	5	Ataxia, diarrhea, polydipsia, polyphagia, polyuria, sedation, vomiting, weakness	Affects esophagus and pancreas Causes gastritis and panniculitis
Felbamate	**10–40 mg/kg** PO Q 8 H	1	Tremors (rare)	Affects liver and bone marrow Causes keratoconjunctivitis sicca
Topiramate	**5–10 mg/kg** PO Q 8–12 H	1	Sedation	May cause urinary calculi
Clorazepate	**0.05–2 mg/kg** PO Q 12 H	3	Ataxia, polyphagia, sedation, weakness	None

** Serum drug monitoring recommended*

TABLE 4. AED Pulse Therapy

DRUG	DOSE	INDICATIONS
PULSE THERAPY		
Gabapentin	**10–30 mg/kg** PO Q 8 H	For as long as patient is at risk for more seizures
Phenobarbital	**4–10 mg/kg** PO	After every seizure (and/or clorazepate); administer up to Q 1 H, not to exceed 30 mg/kg within 12 H
Clorazepate	**0.5–1 mg/kg** PO	After every seizure (and/or phenobarbital)
OTHER		
Acepromazine	**0.5–1 mg/kg** PO[30]	To reduce post-ictal confusion and prevent stress-induced seizures; second dose (0.5 mg/kg) can be given in 1 H if confusion not controlled
Bromide	***Avoid*** for pulse therapy due to its side effects and long elimination half-life	

Although studies are lacking, administration of an extra dose of maintenance AED and initiation of a novel AED for a short period of time (pulse therapy) is advised to control cluster seizures and status epilepticus (**Table 4**).

I advise owners to give a dose of AED used for pulse therapy between seizures to assess side effects, and determine best tolerated dose, prior to using the medication in the post-ictal period.

Other Types of Therapy. Intranasal (IN), subcutaneous (SC), intramuscular (IM), and rectal AED administration have been advocated when (**Table 5**):

- Patient is unable to swallow
- Rapid cessation of seizure activity is required
- Intravenous (IV) route is unavailable.

I advise owners to give levetiracetam (60 mg/kg SC) plus midazolam (0.2 mg/kg IM) *or* diazepam injectable solution (2 mg/kg by rectum). ■

AED Monitoring

Serum drug concentrations can be monitored for many AEDs (**Table 3**). I will assess serum concentrations when:

- Starting a new AED in a difficult to control patient
- Toxicity is suspected at a relatively low dose
- Abandoning an AED due to poor seizure control.

Although uncommon and often not reported, liver, kidney, bone marrow, immune, and urinary calculi problems are possible consequences of AED administration. Therefore, the following are recommended, at minimum, every 6 to 12 months based on therapy and patient needs:

- Physical examination
- Serum biochemical profile
- Complete blood cell count
- Urinalysis.

AED = anti-epileptic drug; CSF = cerebrospinal fluid; EEG = electroencephalography; IE = idiopathic epilepsy; IM = intramuscular; IN = Intranasal; IV = intravenous; MRI = magnetic resonance imaging; MUE = meningoencephalitis of unknown etiology; SC = subcutaneous

View a video showing a seizure in a dog at todaysveterinarypractice.com/resources.asp.

References

1. Podell M, Fenner WR, Powers JD. Seizure classification in dogs from a nonreferral-based population. *JAVMA* 1995; 206(11):1721-1728.
2. Fisher RS, van Emde Boas W, Blume W, et al. Epileptic seizures and epilepsy: Definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia* 2005; 46(4):470-472.
3. Hardy BT, Patterson EE, Cloyd JM, et al. Double-masked, placebo-controlled study of intravenous levetiracetam for the treatment of status

TABLE 5. Other AED Rescue Therapies

DRUG	DOSE	INDICATIONS
Diazepam	**0.5 mg/kg** IN *or* **2 mg/kg** per rectum (injectable solution)	• IN injections reach more rapid, more consistent, and longer lasting serum concentrations than rectal administration[31] • Rectal suppository formulations have unfavorable absorption; not recommended for emergency treatment[32]
Levetiracetam	**60 mg/kg** SC *or* **60 mg/kg** (undiluted) IV bolus	• Reaches therapeutic concentrations ≤ 15 min and lasts 7 H; currently my at-home therapy of choice[33] • IV bolus to rapidly achieve useful serum concentrations without sedation[34]
Midazolam	**0.2 mg/kg** IM ***or*** IN	• Can be used instead of diazepam

epilepticus and acute repetitive seizures in dogs. *J Vet Intern Med* 2012; 26:334-340.
4. Gullov CH, Toft N, Baadsager MM, Berendt M. Epilepsy in the Petit Basset Griffon Vendeen: Prevalence, semiology, and clinical phenotype. *J Vet Intern Med* 2011; 25(6):1372-1378.
5. Hulsmeyer V, Zimmermann R, Brauer C, et al. Epilepsy in border collies: Clinical manifestation, outcome, and mode of inheritance. *J Vet Intern Med* 2010; 24(1):171-178.
6. Jokinen TS, Metsahonkala L, Bergamasco L, et al. Benign familial juvenile epilepsy in Lagotto Romagnolo dogs. *J Vet Intern Med* 2007; 21(3):464-471.
7. Brauer C, Kastner SB, Rohn K, et al. Electroencephalographic recordings in dogs suffering from idiopathic and symptomatic epilepsy: Diagnostic value of interictal short time EEG protocols supplemented by two activation techniques. *Vet J* 2012; 193(1):185-192.
8. Cuff DE, Bush WW, Stecker MM, et al. Use of continuous electroencephalography for diagnosis and monitoring of treatment of nonconvulsive status epilepticus in a cat. *JAVMA* 2014; 244(6):708-714.
9. Deacon C, Wiebe S, Blume WT, et al. Seizure identification by clinical description in temporal lobe epilepsy: How accurate are we? *Neurology* 2003; 61(12):1686-1689.
10. Bush WW, Barr CS, Stecker MM, et al. Diagnosis of rapid eye movement sleep disorder with electroencephalography and treatment with tricyclic antidepressants in a dog. *JAAHA* 2004; 40(6):495-500.
11. Schwartz M, Munana KR, Nettifee-Osborne J. Assessment of the prevalence and clinical features of cryptogenic epilepsy in dogs: 45 cases (2003-2011). *JAAHA* 2013; 242(5):651-657.
12. Song RB, Vite CH, Bradley CW, Cross JR. Postmortem evaluation of 435 cases of intracranial neoplasia in dogs and relationship of neoplasm with breed, age, and body weight. *J Vet Intern Med* 2013; 27(5):1143-1152.
13. Wessmann A, Volk HA, Parkin T, et al. Living with canine idiopathic epilepsy: A questionnaire-based evaluation of quality of life. *ECVN Abstracts* 2012; p 835.
14. Ben-Ari Y, Crepel V, Represa A. Seizures beget seizures in temporal lobe epilepsies: The boomerang effects of newly formed aberrant kainatergic synapses. *Epilepsy Curr* 2008; 8(3):68-72.
15. March PA. Seizures: Classification, etiologies, and pathophysiology. *Clin Tech Small Anim Pract* 1998; 13(3):119-131.
16. Dewey CW. Anticonvulsant therapy in dogs and cats. *Vet Clin North Am Small Anim Prac* 2006; 36(5):1107-1127.
17. Muñana KR. Management of refractory epilepsy. *Top Companion Anim Med* 2013; 28(2):67-71.
18. Rossmeisl JH. Alternative anticonvulsants in dogs and cats. *Clin Brief* 2011; Oct:63-66.
19. Brodie MJ, Kwan P. Staged approach to epilepsy management. *Neurol* 2002; 58(8):S2-S8.
20. Podell M. Seizures in dogs. *Vet Clin North Am Small Anim Pract* 1996; 26(4):779-809.
21. Dewey CW, Boothe DM, Berg JM, et al. Zonisamide therapy in refractory epilepsy in dogs. *JAAHA* 2004; (40):285-291.
22. Dewey CE, Cerd-Gonzalez S, Levine JM, et al. Pregabalin as an adjunct to phenobarbital, potassium bromide or a combination of phenobarbital and potassium bromide for treatment of dogs with suspected idiopathic epilepsy. *JAVMA* 2009; 235(12):1442-1449.
23. Volk HA, Matiasek LA, Feliu-Pascual AL, et al. The efficacy and tolerability of levetiracetam in pharmacoresistant epileptic dogs. *Vet J* 2008; 176:310-319.
24. Muñana KR, Zhang D, Patterson EE. Placebo effect in canine epilepsy trials. *J Vet Intern Med* 2010; 24(1):166-170.
25. Muñana KR, Thomas WB, Inzana KD, et al. Evaluation of levetiracetam as adjunctive treatment for refractory canine epilepsy: A randomized, placebo-controlled, crossover trial. *J Vet Intern Med* 2012; 26(2):341-348.
26. Bateman SW, Parent JM. Clinical findings, treatment, and outcome of dogs with status epilepticus or cluster seizures: 156 cases (1990-1995). *JAVMA* 1999; 215(10):1463-1468.
27. Siato M, Munana KR, Sharp NJ, Olby NJ. Risk factors for development of status epilepticus in dogs with idiopathic epilepsy and effects of status epilepticus on outcome and survival time: 32 cases (1990-1996). *JAVMA* 2001; 219(5):618-623.
28. Howbert JJ, Patterson EE, Stead SM, et al. Forecasting seizures in dogs with naturally occurring epilepsy. *PLoS One* 2014; 9(1):e81920.
29. Patterson EE, Goel V, Cloyd JC, et al. Intramuscular, intravenous and oral levetiracetam in dogs: Safety and pharmacokinetics. *J Vet Pharmacol Ther* 2008; 31(3):253-258.
30. Tobias KM, Marioni-Henry K, Wagner R. A retrospective study on the use of acepromazine maleate in dogs with seizures. *JAAHA* 2006; 42(4):283-289.
31. Platt SR, Randell SC, Scott KC, et al. Comparison of plasma benzodiazepine concentrations following intranasal and intravenous administration of diazepam to dogs. *Am J Vet Res* 2000; 61(6):651-654.
32. Probst CW, Thomas WB, Moyers TD, et al. Evaluation of plasma diazepam and nordiazepam concentrations following administration of diazepam intravenously or via suppository per rectum in dogs. *Am J Vet Res* 2013; 74(4):611.
33. Hardy BT, Patterson EE, Cloyd JM. Subcutaneous administration of levetiracetam in healthy dogs (abst). *J Vet Intern Med* 2011; 25(3):741.
34. Dewey CW, Bailey KS, Boothe DM, et al. Pharmacokinetics of single-dose intravenous levetiracetam administration in normal dogs. *J Vet Emer Crit Care* 2008; 18(2):153-157.

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