



NEUROLOGY

Treatment Plans for Routine and Refractory Canine Epilepsy

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Epilepsy is a common, complex disease in which abrupt, abnormal synchronous or excessive electrical activity in the brain causes seizures. Seizures may manifest as variable motor, autonomic, and/or behavioral clinical signs.¹ The seizures are typically episodic and short but may change in frequency, length, and severity over time. Patients often have a genetic predisposition.²

Treatment is often frustrating and may involve one or multiple anticonvulsant drugs. Taking the time to educate clients on the expectations and goals of therapy will likely increase compliance, help set expectations, and keep lines of communication open. Owners often want a drug to make all seizures go away completely. It must be emphasized that this may not happen and that the goals should be reducing seizure frequency, maximizing quality of life, and minimizing adverse drug effects.³

DIAGNOSIS

Idiopathic/genetic epilepsy is one of the most common causes of seizures in dogs; however, it is a diagnosis of exclusion, and many other possible

causes must be ruled out, if possible. Some of the most common are listed in **BOX 1**. Physical examination, neurologic examination, and additional diagnostic testing—such as complete blood count (CBC), serum biochemistry panels, magnetic resonance imaging (MRI) and/or computed tomography (CT), spinal fluid analysis, and infectious disease testing—are often needed to help identify and/or eliminate these causes (**BOX 2**). Results of these tests are often normal in patients with idiopathic epilepsy.

Referral to a board-certified veterinary neurologist may be necessary. It is common for the diagnosis of idiopathic/genetic epilepsy to be tentative, as many owners resist the expense of advanced imaging.

Box 1 Common Causes of Seizures

- Idiopathic/genetic disease
- Infectious and inflammatory disease
- Neoplastic disease
- Congenital disease
- Metabolic disease
- Vascular disease
- Trauma

PATIENT-FOCUSED TREATMENT

Seizures in dogs with epilepsy may never be completely eliminated, but one of the most important goals is good quality of life for the patient.

**Box 2 Additional Diagnostic Tests in Dogs With Seizures⁴**

- Blood pressure
- Ocular examination
- Liver function tests (pre- and postprandial bile acids, ammonia)
- Full thyroid panel
- Glucose or fructosamine level
- Serologic tests for specific infectious organisms based on history, signalment, and exposure to endemic areas
- Vitamin B₁₂ level
- Ionized calcium level
- Tests for specific toxins
- Electroencephalography

In a recent study, diagnosis of idiopathic epilepsy required a dog to have 2 or more seizures of intracranial/cerebral origin occurring more than 24 hours apart, as well as normal physical and neurologic examination findings between seizures.⁵ Results of minimum database testing, including a CBC, serum biochemistry panel, and urinalysis, had to be normal. In addition, seizure characteristics were required to be identical from seizure to seizure.⁵ The International Veterinary Epilepsy Task Force (ivetf.org) recently proposed criteria for the diagnosis of idiopathic epilepsy (**BOX 3**).⁴

A thorough history should be obtained from the owner, including age at onset, duration and frequency of seizures, and length of postictal period. The owner should also be asked to provide a detailed description of the seizures (e.g., paddling with potential increased muscle tone, particularly in the limbs; loss of consciousness; urinating, defecating, hypersalivating).

Neurologic Examination

Interictal neurologic examination findings are generally normal in dogs with idiopathic epilepsy.

Minimum Database Tests

A CBC, serum biochemistry profile, urinalysis, and total thyroxine (T₄) test should be performed to look for underlying disease that may suggest a cause for the

seizures or that could alter the treatment plan (e.g., significant renal or hepatic disease).

Conventional Imaging

Thoracic and/or abdominal radiography and/or abdominal ultrasonography should be performed if clinically indicated.

Cross-sectional Imaging

Cross-sectional imaging (MRI and/or CT) should be performed, if possible, to verify that there are no structural lesions in the brain. MRI has a much greater range of soft tissue contrast and can show detailed brain anatomy in 3 planes without moving the patient. Overall, it is more sensitive than CT for abnormalities within the brain. However, CT is much faster than MRI and is typically less expensive.

Box 3 International Veterinary Epilepsy Task Force Confidence Level for Diagnosis of Idiopathic Epilepsy^{4,a}**Tier 1**

- Reported history of 2 or more seizures at least 24 hours apart
- Age at onset: 6 months to 6 years
- Normal physical examination findings between seizures
- Normal neurologic examination findings between seizures
- Generally unremarkable minimum database results
- Family history
- Possible additional laboratory testing: liver function testing (bile acids, ammonia), thyroid panel

Tier 2

- Tier 1 factors
- Unremarkable pre- and postprandial bile acid results
- Brain MRI (if seizure-related changes found on MRI, repeat MRI after 16-week interictal period, if possible)
- Cerebrospinal fluid analysis

Tier 3

- Tier 1 and Tier 2 factors
- Electroencephalographic abnormalities

^aTiers reflect increasing levels of confidence in the diagnosis. In the clinical setting, diagnosis based on Tier 1 factors only is common.

Cerebrospinal Fluid Analysis

Sampling of cerebrospinal fluid via cisterna magna or lumbar cisternal puncture may be helpful in identifying and/or eliminating infectious/inflammatory causes of seizures. Cerebrospinal fluid samples can be submitted for polymerase chain reaction and titer testing.

TREATMENT

The administration of anticonvulsant medication is the foundation of therapy.⁶ The goal of this therapy is to reduce the frequency, length, and severity of seizure activity as much as possible.³ This must be accomplished while minimizing adverse drug-related effects. Epileptic dogs that are either not treated or treated inappropriately may have an increase in seizure frequency, duration, or severity over time.³

While many owner and patient factors may come into play, the International Veterinary Epilepsy Task Force recommends beginning maintenance anticonvulsant therapy when a dog experiences any one of the following:⁶

- Two or more seizures within a 6-month period
- Status epilepticus
- Cluster seizures
- A severe or lengthy postictal period
- Increasing seizure frequency and/or length
- Increasing seizure severity

Currently, evidence-based guidelines regarding the choice of anticonvulsant medication in dogs are limited. **BOX 4** lists factors to consider when choosing a medication.⁶ Ultimately, each dog is managed on a case-by-case basis (**FIGURE 1**). Some dogs with acceptable seizure control may have serum drug concentrations below the lower limit of the reported

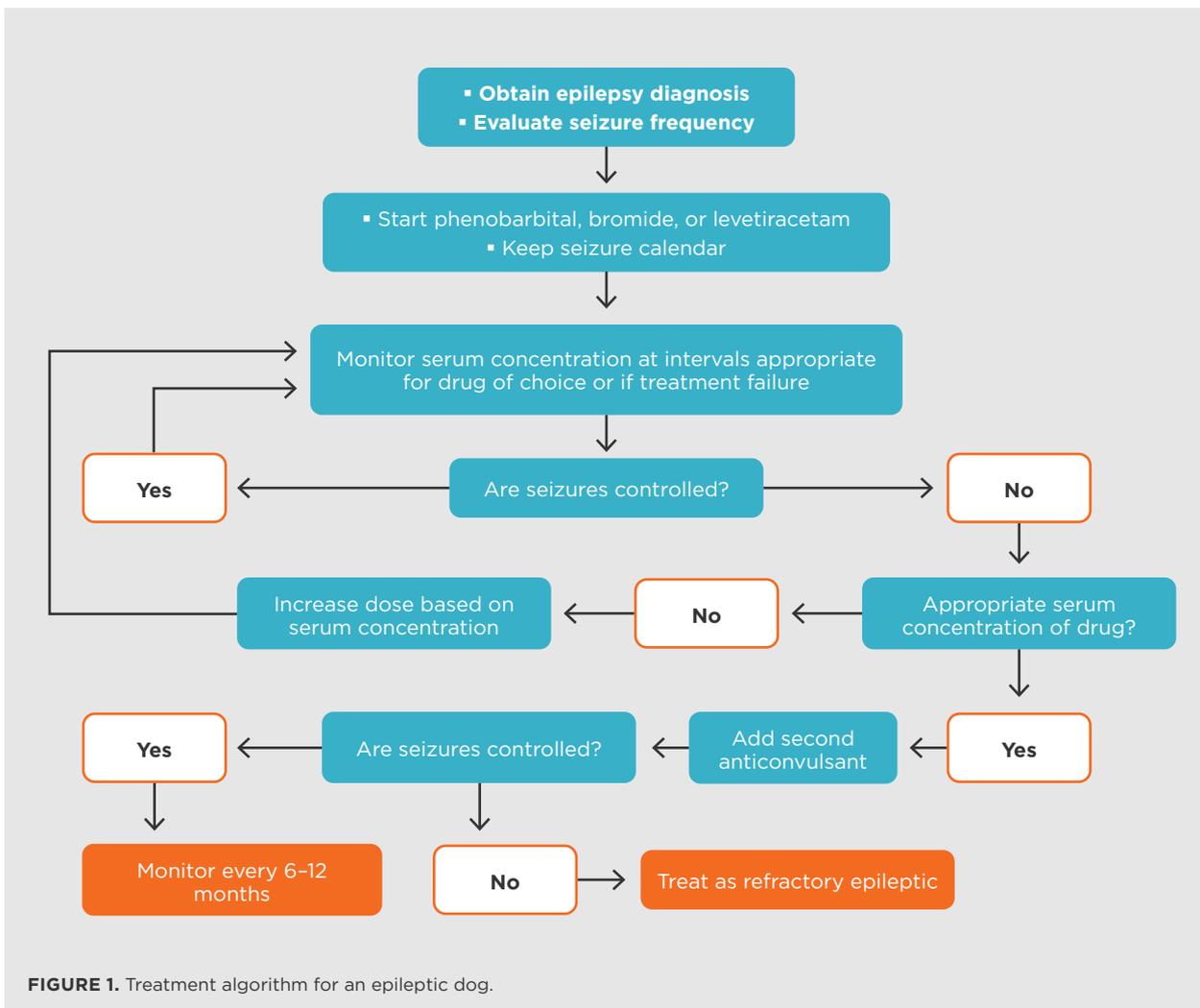


FIGURE 1. Treatment algorithm for an epileptic dog.



Box 4 Considerations for Choosing Anticonvulsant Medication in Dogs⁶

Drug factors

- Safety
- Ease of administration
- Side effects
- Interactions with other medications
- Half-life (as related to dosing frequency)
- Regulatory issues (e.g., approved in dogs, controlled)

Patient factors

- Underlying disease (e.g., renal, hepatic)
- Owner's lifestyle (ability to dose, ability to dose on time, finances)
- Seizure frequency

therapeutic range. This finding does not necessarily require adjustment of the drug dose or dosing interval, as this serum concentration may be adequate for that individual.⁶

Routine Epilepsy

A typical patient with nonrefractory epilepsy can often be managed with monotherapy. In some cases, over time, addition of a second anticonvulsant may be needed. Dosing adjustments are made as needed pending the patient's clinical status, response to medication, and potential side effects. The following drugs are commonly used in the treatment of uncomplicated epileptic seizures in dogs. **TABLE 1** summarizes recommended starting doses.

The 2015 American College of Veterinary Internal Medicine (ACVIM) consensus statement on seizure management in dogs recommends phenobarbital or potassium bromide as initial treatment, as both drugs have been shown to be highly effective.¹⁰ The author typically starts medication-naïve dogs on phenobarbital monotherapy first, after fully evaluating the dog for liver or other concurrent disease.

Phenobarbital

Phenobarbital, after many years of use, was approved for the treatment of epilepsy in dogs in 2009. Its side effects are well documented, and it is relatively safe.⁶ Short-term side effects include polydipsia/polyuria, lethargy, increased appetite, and ataxia.⁶ Rarely, more

serious effects, including bone marrow suppression and severe hepatic injury, may occur. Phenobarbital is therefore not recommended in dogs with hepatic dysfunction.⁶ Phenobarbital is available in both tablet and parenteral form. A 2012 study demonstrated that phenobarbital is effective in reducing seizure frequency in 85% of dogs with idiopathic epilepsy when plasma concentrations of 20 to 30 mg/L are maintained.¹²

The recommended starting oral dose of phenobarbital in dogs is 2 to 3 mg/kg q12h.^{3,6} A recent study showed that a 3-times-per-day regimen may be beneficial in some dogs.¹³ The dose must be tailored to the individual patient based on seizure control, serum blood levels, and side effects.⁶ Dogs presenting in status epilepticus or with cluster seizures may be loaded on phenobarbital at 15 to 20 mg/kg IV, IM, or PO (given as a single dose or divided).⁶ Divided dosing is preferred to avoid possible cardiorespiratory depression.

Serum concentration should be monitored at 2 to 3 weeks after beginning therapy and any time there is a change in dose or treatment failure. Routine monitoring, including CBC, serum biochemistry, and phenobarbital level, should be performed every 6 months.^{3,6} A 2000 study demonstrated that, owing to phenobarbital's long half-life, the timing of blood sample collection is not important in most epileptic dogs. A trough level could be collected immediately before administering the next scheduled dose.¹⁴ Common biochemical changes include increased serum alkaline phosphatase, cholesterol, and triglycerides.⁶ Bile acid testing should be performed if there is any concern for hepatic dysfunction.³ Serum separator tubes should not be used.³ Practitioners should be aware that serum thyroid levels may be low.⁶

Phenobarbital can affect the disposition of concurrent medications that are also metabolized by the cytochrome P450 family. This includes other anticonvulsants as well as antibiotics and many other drugs.

Levetiracetam

Levetiracetam is a newer anticonvulsant drug that has been shown to reduce seizure frequency in some dogs. It is generally well tolerated, and side effects are rare. They may include ataxia, mild sedation, inappetence, and vomiting.⁷ Levetiracetam is available in both immediate- and extended-release formulations, as well as a liquid. A 2012 study evaluating levetiracetam as an add-on medication showed a decrease in seizure

frequency when compared with baseline; however, there was no difference in seizure frequency when compared with placebo.⁷ Levetiracetam may also be used as pulse treatment for cluster seizures.¹⁵

The recommended starting oral dose of levetiracetam in dogs is 20 mg/kg 3 to 4 times per day.^{3,7} Four times per day is often not feasible for owners. When using the extended-release form, the author recommends a starting dose of 30 mg/kg q12h.⁸ If seizure control is ineffective, the dose may be increased by 20 mg/kg increments until seizure control is achieved, side effects occur, or the cost of the drug is too high for the client.³ If needed, levetiracetam can also be administered parenterally.⁶ When given concurrently with phenobarbital and/or potassium bromide, dosage increases in levetiracetam may be necessary, as levetiracetam clearance is increased when given with one or both of these drugs.¹⁶ Serum concentration measurement can help guide treatment.¹⁶ However, therapeutic guidelines have not yet been established in dogs and are currently deduced from human literature.

Zonisamide

Zonisamide is a newer sulfonamide anticonvulsant medication. It is generally well tolerated and is considered safe when used at recommended doses. Reported side effects of this drug include vomiting and ataxia.¹⁷ Isolated cases of acute hepatic necrosis, renal tubular acidosis, and erythema multiforme associated with zonisamide use have been reported in the literature.¹⁸⁻²⁰ A 2004 study demonstrated that zonisamide was effective in controlling seizures in a small cohort of adult dogs with refractory idiopathic epilepsy, with 58% of dogs having significantly reduced seizure frequency when zonisamide was used as an add-on anticonvulsant.¹⁷ A 2013 study showed that zonisamide was effective as monotherapy in 6 out of 10 dogs.²¹

The recommended starting dose is 5 mg/kg PO q12h in dogs not receiving phenobarbital and 10 mg/kg PO q12h in dogs receiving phenobarbital.⁹ The drug may be used alone or as an add-on agent.¹⁷ Therapeutic monitoring levels have not yet been established in dogs.

Bromide

Bromide is a salt that has been shown to be effective as both add-on therapy and monotherapy.^{3,22} Up to 83% of dogs were shown to have a reduction in seizure occurrence compared with the equivalent time period

before beginning bromide.²² Bromide is most commonly administered as potassium bromide and is generally well tolerated, with reported side effects including pelvic limb ataxia, polyuria/polydipsia, increased appetite, sedation/lethargy, nausea and vomiting, pancreatitis (less common), and aggressive behavior (less common).³

The recommended starting dose for bromide is 40 mg/kg/day as monotherapy and 15 to 20 mg/kg/day as add-on therapy.^{6,10} The dose is often divided to reduce the chance of stomach upset. A higher loading dose may be used to achieve steady-state therapeutic concentration sooner.^{3,6} There are many suggested schemes for loading bromide in current literature and drug formularies.

Sodium bromide contains more bromide on a weight basis; as such, the dose should be decreased by 15% compared with potassium bromide.^{3,6}

Serum concentration is recommended to be checked at 8 to 12 weeks (or after loading protocol) and then on a 6- to 12-month basis.^{3,6,10}

Gabapentin

Gabapentin is used as a pain-relieving medication and anticonvulsant. A 2005 study investigated gabapentin as an add-on anticonvulsant in dogs with refractory seizures and found that in a 4-month period, 3 of 17 dogs were seizure-free and 4 other dogs had a 50% reduction in seizure frequency. However, these differences were not statistically significant.²³ Gabapentin is generally well tolerated in dogs, and the most commonly reported side effects are sedation/lethargy and pelvic limb ataxia.⁹

A recommended initial dose is 20 mg/kg q8h.^{3,6} However, there is a very wide dose range of 10 to 60 mg/kg that may be divided into doses given every 6 to 8 hours.^{6,11}

Benzodiazepines

Benzodiazepine drugs used in dogs with seizures include diazepam, midazolam, clorazepate, and clonazepam.³ In general, they are not recommended for chronic administration in dogs due to tolerance and the tendency for the seizures to become refractory.^{3,9} The author has found the use of oral clorazepate pulse therapy (**TABLE 1**) to be effective in some dogs with



cluster seizures. Injectable diazepam and midazolam are commonly used for the immediate treatment of an active seizure. Midazolam can also be administered intranasally via an atomizer (**FIGURE 2**).

Refractory Epilepsy

Refractory (i.e., drug-resistant) epilepsy is particularly challenging for both the veterinarian and the owner. Treatment can become difficult in terms of drug selection, drug dose, and dosing schedule. Epilepsy is considered refractory when 2 (or more) appropriate anticonvulsant medications have failed to give adequate seizure control despite serum concentrations in the standard therapeutic range.^{17,24} This occurs in 20% to 40% of all dogs with epilepsy.^{7,24}

Treatment options include the use of additional anticonvulsant medications (polytherapy) and nonpharmacologic approaches. Polytherapy may involve drugs listed above that were not used as first-line therapy and/or pregabalin, imepitoin, felbamate, and others. Polytherapy is recommended when monotherapy or ditherapy fails and/or the dog experiences cluster seizures or status epilepticus.

Treating refractory epilepsy begets many potential problems, including medication cost, frequent clinic visits for monitoring/laboratory tests, concerns for increased adverse effects and drug interactions, and confusion in dosing schedules. Furthermore, with some of the newer drugs, studies demonstrating efficacy and evaluating long-term safety are limited.⁹

In addition, not all refractory cases are truly refractory. There are many reasons why seizures may be difficult to control. A patient may have been misdiagnosed, may



FIGURE 2. Intranasal midazolam atomizer for at-home use for seizures (Teleflex Medical, teleflex.com).

not be having seizures at all, may be on the incorrect drug or incorrectly dosed, or may have poor owner compliance.⁹ Serial monitoring of serum anticonvulsant concentration may help identify problems.

Unfortunately, there are dogs for whom seizure control is never achieved. These dogs are often euthanized for poor quality of life. The author typically exhausts the medications discussed above before moving on to the following medications.

Pregabalin

Pregabalin is structurally similar to gabapentin. A 2009 study showed that the most common side effects were sedation and ataxia.²⁵ This study suggested that pregabalin may be effective as an add-on anticonvulsant in poorly controlled dogs already on standard treatment.²⁵

The recommended starting oral dose in dogs is 2 to 4 mg/kg 2 to 3 times daily, starting at the low end of

TABLE 1 Recommended Oral Starting Dosages for Commonly Used Anticonvulsants

DRUG	DOZSAGE
Phenobarbital ⁶	2-3 mg/kg q12h
Levetiracetam (regular release) ^{3,7}	20 mg/kg 3 to 4 times per day
Levetiracetam (extended release) ⁸	30 mg/kg q12h
Zonisamide ⁹	Dogs not receiving phenobarbital: 5 mg/kg PO q12h Dogs receiving phenobarbital: 10 mg/kg PO q12h
Bromide ^{6,10}	Monotherapy: 40 mg/kg/day after loading dose, if necessary Add-on therapy: 15-20 mg/kg/day
Gabapentin ^{3,6}	10-20 mg/kg q8h
Clorazepate (pulse therapy)	0.5-1 mg/kg ¹¹ within 24 hours after the first seizure and continued q8h until the dog is seizure-free for 24 hours

the dosing range and increasing 1 mg/kg per week until the final dose is reached.²⁵ In patients with renal disease, lower doses are recommended.

Imepitoin

Imepitoin was approved for use in dogs with epilepsy in Europe in 2013.²⁶ In 2018, it was approved by the U.S. Food and Drug Administration for the treatment of noise aversion in dogs.²⁷ Possible side effects most commonly included polyphagia and, rarely, gastrointestinal signs, hyperactivity, ataxia, and prolapsed third eyelid.²⁶ In a recent study, most dogs with idiopathic epilepsy were controlled successfully with imepitoin compared with phenobarbital.²⁶

The recommended starting dose is 10 to 20 mg/kg q12h.⁶ The dose can be increased up to a maximum of 30 mg/kg q12h.⁶

A CBC and serum biochemistry profile are recommended before starting imepitoin treatment and every 6 to 12 months thereafter.⁶

Topiramate

Topiramate is a relatively newer drug used in the treatment of epilepsy in humans.⁶ A 2013 study in 10 dogs showed that the drug was generally well tolerated, with side effects including ataxia, sedation, and weight loss.²⁸ This same study suggested that topiramate may be effective as an add-on medication for the treatment of idiopathic epilepsy in dogs.

A suggested starting dose is 2 mg/kg PO q12h.²⁸ This dose may be slowly increased to 5 to 10 mg/kg 2 to 3 times per day depending on the patient's response.²⁸

Felbamate

Felbamate is an anticonvulsant introduced in 1993 for use in humans. A 1996 ACVIM abstract showed that 12 of 16 dogs had improved seizure control on felbamate. However, 4 of the responders developed liver disease. This study concluded that felbamate is a useful add-on anticonvulsant, but liver dysfunction can occur when given with other anticonvulsants.²⁹

In a 2001 study of 6 dogs, adverse effects included keratoconjunctivitis sicca, thrombocytopenia, leukopenia, and lymphopenia.³⁰

Felbamate should only be used in dogs refractory to other, more thoroughly researched, anticonvulsants.⁶ In humans, it has been associated with potentially serious adverse effects, including aplastic anemia and hepatotoxicity.⁹ If possible, felbamate should not be used in dogs with hepatic disease.⁶

A suggested starting dose is 15 mg/kg q8h.⁹

A CBC and serum biochemistry panel (particularly liver enzymes) should be performed at the start of therapy and every month for the first 6 to 12 months.⁶ After that, monitoring every 6 to 12 months is recommended. It has been shown that felbamate increases the serum concentration of phenobarbital in a dose-dependent manner, making this monitoring extremely important.³¹

Alternative Treatments

The ineffectiveness of the above treatments in a certain percentage of dogs may spark owners to look for alternative treatments.³²

Cannabidiol Oil

Cannabidiol (CBD) is an extract of the cannabis plant and, along with tetrahydrocannabinol (THC), is one of the most abundant cannabinoids.³² Unlike THC, CBD is nonpsychotropic and is associated with pain relief. A 2019 study conducted at Colorado State University suggested that CBD oil may help reduce seizures in dogs with epilepsy.³² The study showed a significant reduction in seizure frequency (33%) in dogs given CBD oil compared with dogs in the placebo group. However, 50% of dogs in both groups were considered responders; that is, they had a 50% decrease in seizure activity. Serum alkaline phosphatase levels were significantly increased in the CBD group.³² Side effects included ataxia. Further studies are ongoing.

Nonpharmacologic Options

Nonpharmacologic treatments are available. They include vagal nerve stimulation, alterations in diet, acupuncture, and other homeopathic remedies.¹⁰ A 2015 study showed evidence that feeding a medium-chain triglyceride diet may reduce seizure frequency in dogs and play a role in the overall seizure management plan.³³ Information on vagal nerve stimulation, acupuncture, or specific homeopathic remedies in the treatment of dogs with epilepsy is limited.



CONCLUSION

The definition of successful seizure control varies between clinicians. Seizures in dogs with epilepsy may never be completely eliminated. Acceptable goals may include longer interictal period (decreased frequency), decreased severity, decreased duration, or moving from cluster seizures to single isolated events. One of the most important goals is good quality of life for the patient.¹⁰ Client communication and the setting of realistic expectations are key to the management of these patients. Phenobarbital and bromide are still considered to be effective first-line choices, but many alternatives exist. Some cases may benefit from referral to a veterinary neurologist. **TVP**

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CONTINUING EDUCATION

Treatment Plans for Routine and Refractory Canine Epilepsy

TOPIC OVERVIEW

This article provides an overview of canine epilepsy, including diagnosis, treatment for routine and refractory epilepsy, commonly used anticonvulsant drugs and their recommended starting doses, and a brief introduction to new medications and alternative therapies.

LEARNING OBJECTIVES

After reading this article, readers should be able to identify both routine and difficult-to-treat epileptic dogs in their practices. Readers should also gain an understanding of anticonvulsant therapies available for treating epileptic dogs.

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- Anticonvulsant, or antiepileptic, drugs eliminate seizures in all dogs.
 - True
 - False
- The typical age at onset (first seizure) in an epileptic dog is _____.
 - <6 weeks
 - Between 6 months and 6 years
 - Between 5 and 10 years
 - >10 years
- Why is it important to rule out other causes of seizures before diagnosing epilepsy?
 - To look for underlying disease and treat it if found
 - To look for concurrent diseases (e.g., renal or hepatic) that could alter the treatment plan
 - a and b
- Which of the following is not considered a reason to start maintenance anticonvulsant therapy in a dog with epileptic seizures?
 - Two or more seizures within a 6-month period
 - Seizures becoming less severe
 - Lengthy postictal period
 - Increasing seizure frequency and/or length
- Epilepsy is considered refractory when
 - Two (or more) appropriate anticonvulsant medications have failed to give adequate seizure control.
 - Serum concentrations are below the standard therapeutic range for a given drug.
 - The patient has <1 seizure every 6 months.
 - The patient is appropriately controlled on 1 anticonvulsant medication.
- Which 2 medications are still considered to be first-line anticonvulsant medications for epileptic dogs?
 - Phenobarbital and bromide
 - Phenobarbital and gabapentin
 - Felbamate and topiramate
 - Bromide and gabapentin
- _____ is commercially available in regular- and extended-release formulations.
 - Gabapentin
 - Bromide
 - Zonisamide
 - Levetiracetam
- _____ has been approved in Europe for use in dogs with seizures and in the U.S. for use in dogs with noise aversion.
 - Levetiracetam
 - Topiramate
 - Imepitoin
 - Phenobarbital
- Polytherapy is recommended to treat epilepsy in dogs that
 - Are not controlled with monotherapy or ditherapy.
 - Experience cluster seizures.
 - Experience status epilepticus.
 - All of the above
- In preliminary studies of use of CBD oil for the management of seizures in dogs, which liver enzyme was elevated in the CBD oil group compared to the control group?
 - Alkaline phosphatase
 - Alanine aminotransferase
 - Aspartate aminotransferase
 - Bilirubin