

ACVIM Consensus Statement

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2015 ACVIM Small Animal Consensus Statement on Seizure Management in Dogs

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This report represents a scientific and working clinical consensus statement on seizure management in dogs based on current literature and clinical expertise. The goal was to establish guidelines for a predetermined, concise, and logical sequential approach to chronic seizure management starting with seizure identification and diagnosis (not included in this report), reviewing decision-making, treatment strategies, focusing on issues related to chronic antiepileptic drug treatment response and monitoring, and guidelines to enhance patient response and quality of life. Ultimately, we hope to provide a foundation for ongoing and future clinical epilepsy research in veterinary medicine.

Key words: Cerebrospinal fluid; Dogs; Epilepsy; Magnetic resonance imaging; Neurologic disorder.

Epileptic seizures are a common neurologic disorder in dogs characterized by a wide spectrum of clinical signs and consequences. Variable short- and long-term morbidity effects occur caused both by the disease and its treatment. Survivability often is dependent more on quality of life and financial issues than actual disease

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Abbreviations:

AED	antiepileptic drugs
ESVN/ECVN	European Society and College of Veterinary Neurology
ACVIM	American College of Veterinary Internal Medicine
MRI	magnetic resonance imaging
CT	computer tomography
CSF	cerebrospinal fluid
CNS	central nervous system
ACTH	adrenocorticotrophic hormone
t4	thyroxine
MCT	medium chain triglyceride
QOL	quality of life

manifestations.^{1,2} As such, the burden is on the clinician to balance the variable outcome measures of seizure control and owner perception of patient quality of life.

Epilepsy is a heterogeneous disease process complicated by the inability to obtain a definitive diagnosis for all patients as a consequence of the challenges of limited diagnostic testing because of financial constraints, unpredictability of disease progression, and gaps in scientific knowledge of disease pathophysiology.^{3–5} Lack of uniformity of accepted definitions for seizure type, diagnosis, and treatment are being addressed but are complicated by wide variations in treatment strategies between primary and specialty clinicians alike. Furthermore, a relatively small database of strong evidence-based clinical studies exists for the ever-changing number of antiepileptic drugs (AED) designed for human use. As a result, many primary care clinicians are left to treat epilepsy with lack of uniform, scientifically based guidelines.

The International Veterinary Epilepsy Task Force recently published collaborative consensus statements

on epilepsy classification³, diagnostic approaches,⁶ treatment,⁷ and therapeutic outcome measures.⁴ These papers have created a working foundation for the advancement of veterinary epileptology.

The purpose of this paper was to build on previous work by providing a scientific and working clinical consensus statement on seizure management in dogs based on current literature coupled with clinical expertise. The goal is to establish guidelines for a predetermined, concise, and logical sequential approach to seizure management starting with seizure identification and diagnosis (not included in this report), reviewing decision-making, treatment strategies, focusing on issues related to chronic AED treatment response and monitoring, and concluding with guidelines to enhance patient response and quality of life. Ultimately, we hope to provide a foundation for ongoing and future clinical epilepsy research in veterinary medicine.

Methodology

The consensus was reached based on the available published evidence in the peer-reviewed literature, including proceedings of Annual Congresses of the European Society and College of Veterinary Neurology (ESVN / ECVN) and the American College of Veterinary Internal Medicine (ACVIM). Aside from searching the standard electronic databases Pub Med (www.ncbi.nlm.nih.gov/PubMed), CAB Abstracts (www.cabdirect.org), and Web of Science (<http://wok.mimas.ac.uk>), search strategies included reference lists of published papers and proceedings of the aforementioned relevant scientific conferences. Studies were included following modified criteria previously laid out in detail.⁸ and included any peer-reviewed study without language restrictions in which an AED was used and dogs were diagnosed with presumptive idiopathic epilepsy. The diagnosis of idiopathic epilepsy was considered likely when the dogs were between the ages of 6 months and 6 years, had no interictal neurologic deficits, and metabolic causes were excluded.⁹⁻¹¹ Advanced brain imaging (magnetic resonance imaging [MRI], computer tomography [CT]), cerebrospinal fluid (CSF) analysis, or some combination of these was preferable, but not essential. Data of dogs in which epilepsy was caused by an identifiable cause were not considered. Any form of treatment, including medical and alternative therapies (see supplementary file), were included in this statement. The ACVIM consensus panel based its recommendation for clinical practice on the current published evidence using the criteria with 4 levels of recommendations based on scientific merit and expert panel consensus^{8,12} (Table 1).

When Should Treatment Be Started?

The decision to start AED treatment is based on a number of factors, including etiology, risk of recurrence, seizure type, tolerability, and adverse effects. Risk factors for seizure recurrence are not well established for cats and dogs. A number of relative risk factors

have been identified in epileptic people, including a diagnosis of current or previously defined cerebral lesions or trauma, presence of interictal EEG epileptic discharges (up to 90% recurrence rate) and a history of marked postictal adverse effects.^{13,14} Evidence-based guidelines from several international groups are well established for people based on risk-benefit ratio and predictability factors of drug effect.¹⁵⁻¹⁷ From these guidelines, several commonalities exist in guiding clinical practice including confirmation of an epileptic seizure event and seizure type, obtaining a definitive diagnosis, knowledge that recurrent seizure activity is correlated with poorer long-term treatment success, and the influence of treatment on quality-of-life (QOL) factors.¹⁸ Thus, the decision to treat is a reflection of the treatment goals to decrease or eliminate epileptic events, decrease seizure severity, avoid adverse effects, and decrease seizure-related mortality and morbidity.^{7,19,20}

Although similar information is not as readily available for dogs, extrapolation can provide rational treatment guidelines. Overwhelming evidence exists in people that there is no benefit to starting treatment after a single unprovoked event.¹⁴ The earlier AED treatment is started; however, the better the potential outcome may be for seizure control.²¹⁻²³ Recurrent epileptic seizures can increase epileptogenesis and drug resistance in a subgroup of patients.^{24,25} Prolonged and acute repetitive seizures can increase patient morbidity and require prolonged hospitalization with associated financial burden. Comparable information is not available for dogs.

The panel recommendations to initiate AED treatment are summarized as follows: (i) Identifiable structural lesion present or prior history of brain disease or injury; (ii) Acute repetitive seizures or, status epilepticus (ictal event ≥ 5 minutes or ≥ 3 or more generalized seizures within a 24-hour period); (iii) ≥ 2 or more seizure events within a 6-month period; and (iv) Prolonged, severe, or unusual postictal periods.

Which Drug Should Be Used First?

Selection of AED is based on a number of factors, including seizure type, efficacy, and tolerability. No evidence exists that any single AED provides a better outcome for adults with unprovoked epilepsy when early treatment is started in people.¹⁸ Drug selection, therefore, is often based on tolerability in both people and dogs. The panel recommendations are summarized in Table 1.

Phenobarbital

Phenobarbital is a phenyl barbiturate with the longest history of chronic use of all AEDs in veterinary medicine. Phenobarbital has high bioavailability, being rapidly absorbed within 2 hours and with maximal plasma concentration being achieved within 4-8 hours after PO administration.²⁶ Approximately 50% of the drug is protein bound. The majority of phenobarbital is

Table 1. ACVIM panel recommendations of AED use, monitoring, and risk profile.

Drug	Monotherapy recommendation		Monitor drug levels	Risks Types				Add-on AED recommendation	
	Level	Grade		1	2	3	4	Level	Grade
Phenobarbital	I	A	Y	Y	Y	Y	N	IV	B
Bromide	I	B	Y	Y	Y	Y	N	II	B
Primidone	II	D	Y	Y	Y	Y	N	II	D
Imepitoin	I	A	N	Y	N	N	N	III	C
Levetiracetam	IV	C	N	Y	N	N	N	Ib	B
Zonisamide	III	C	Y	Y	Y	N	N	III	B

Level of study design

Level I and Ib Appropriately designed, controlled trials

1 Criteria

- a I: Blinded, randomized clinical trials and drug efficacy of $\geq 50\%$ for at least 6 months
- b Ib: Blinded, randomized clinical trials and drug efficacy of $\geq 50\%$ for less than 6 months

Level II: Case-control or cohort studies

1 Criteria:

- a Nonblinded, randomized, or nonblinded and nonrandomized clinical trials with cohort size of 15 or more, drug efficacy of $>$ or equal to 50% for $>$ 12 weeks, or both.

Level III: Case reports or series

- 1 Based on individual case reports, conference proceedings, and/or other media distribution as a *potentially* effective and/or predictable outcome

2 Criteria:

- a Nonblinded and nonrandomized clinical trials with cohort size of less than 15 and/or drug efficacy of $\geq 50\%$ for $>$ 12 weeks

Level IV: Expert opinion only

- 1 Based on any level of scientific information as an unestablished, ineffective, and/or harmful
- 2 Criteria: Expert opinion only without documentation of cohort studies

Grade of ACVIM panel recommendation

- 1 A: High recommendation and likely be effective treatment
- 2 B: Moderate recommendation and most likely to be effective treatment
- 3 C: Low recommendation and may not be effective treatment
- 4 D: Not recommended for treatment and may be ineffective and/or dangerous to the patient

metabolized by the liver, with approximately one third excreted unchanged in the urine. Phenobarbital is an auto-inducer of hepatic microsomal enzymes (p450 system), which can progressively decrease the elimination half-life with chronic dosing.^{26–28} Overall, phenobarbital is a relatively inexpensive, well-tolerated drug that can be administered twice daily at a starting dosage of 2.5 mg/kg PO q12 h.²⁶

Variable monotherapy efficacy for seizure reduction was evaluated in 8 studies for a total of 311 dogs.^{29–35} Twenty or more dogs were evaluated in each of 5 studies^{31–35} evaluating a total of 289 dogs treated from 5 to 32 months in 3 of the studies^{31,32,35} with undocumented duration in 2 studies^{29,33}. The cumulative success rate of $>50\%$ seizure reduction to improve seizure control was 82% (258/311 dogs), with a cumulative seizure-free rate of 31% (93/311) and failure rate (no improvement) of 15% (48/311).

Potassium Bromide

Bromide was the first documented AED used for epilepsy in people in 1857 with introduction to veterinary medicine in the 1980s. Bromide typically is given

as the inorganic salt potassium bromide, usually as a solution of 200–250 mg/mL dissolved in double-distilled water. In the United Kingdom, several approved commercial formulations are available. A starting dosage of 40 mg/kg/day potassium bromide is recommended. Bromide is slowly metabolized in the dog with median elimination half-life of 15.2 days and steady-state concentrations of 2450 mg/l. The apparent total body clearance is 16.4 mL/kg/day and the volume of distribution is 0.40 L/kg.³⁶ Steady-state concentrations fluctuate among dogs, most likely as a result of individual differences in clearance and bioavailability. Dietary factors also alter serum drug concentrations, with high chloride diets resulting in excessive renal excretion and lower serum concentrations.³⁷ The drug is excreted in the urine without known hepatic metabolism or toxicity.

Evaluation of bromide monotherapy efficacy was found in only a single study³⁴ in which 73.9% (17/23) of dogs had $>$ 50% seizure reduction and 52% (12/23 dogs) were seizure-free during the 6-month treatment period. The remaining studies focused on the efficacy of potassium bromide as an additional drug with phenobarbital, primidone, or both.^{31,32,34,38–40}

Primidone

Primidone is the only AED that is specifically approved for dogs in the United States, whereas phenobarbital, imepitoin, and (as an additional drug) potassium bromide are approved for treatment of epilepsy in dogs in Europe. Orally administered primidone is rapidly metabolized to its major active metabolite phenobarbital.⁴¹ Experimental studies in dogs indicated that phenobarbital is responsible for more than 85% of the total anticonvulsant activity during continued administration of primidone.⁴¹ In a prospective randomized clinical trial, in which the efficacy of phenobarbital and primidone against epilepsy in dogs was compared, 35 dogs with generalized tonic-clonic seizures were treated for a minimum of 6 months with either drug.⁴² Forty percent of the dogs became seizure-free during treatment with phenobarbital compared to only 25% with primidone. Furthermore, primidone was less well tolerated in dogs than phenobarbital.³⁰ In a retrospective trial in 65 epileptic dogs, primidone and phenobarbital were reported to exert similar efficacy, but important details of study design were not reported.⁴³ In a retrospective comparison of phenobarbital and primidone in 70 newly diagnosed epileptic dogs with different causes of epilepsy, in which the animals were treated for at least 3 months, only 20% of phenobarbital-treated dogs became seizure-free compared to 15% of those treated with primidone.^{32,33} Switching phenobarbital-resistant dogs to primidone did not result in improved seizure control, indicating that there is no advantage to the use of primidone over the use of phenobarbital for the control of seizures in most dogs.⁴⁵

Imepitoin

Imepitoin was approved in Europe for treatment of idiopathic epilepsy only in dogs in 2013, in Australia in 2015 and is currently unavailable in the United States. Imepitoin has a novel and selective mechanism of action that potentiates GABAergic inhibition by acting as a low-affinity, low-efficacy partial agonist at the benzodiazepine site of the GABA_A receptor, although it differs in chemical structure from benzodiazepines.⁴⁴ In a pivotal multi-center clinical field trial, imepitoin was compared with phenobarbital in 226 epileptic dogs in a randomized blinded parallel group design.³⁵ The administration of imepitoin twice daily in incremental dosages of 10, 20, or 30 mg/kg was as effective as phenobarbital in controlling generalized seizures in dogs, but the frequency of adverse events including somnolence or ataxia, polydipsia and increased appetite was significantly higher in the phenobarbital group. These results indicated that imepitoin is a potent and safe first-line AED for epileptic dogs.

Several other trials have been performed in dogs including: (i) a randomized controlled blinded trial in which imepitoin was compared with a pseudoplacebo (ie, low dose of imepitoin); (ii) a randomized blinded trial in which imepitoin was compared with primidone; (iii) an exploratory trial comparing imepitoin with

phenobarbital and primidone in newly diagnosed dogs with epilepsy; and, (iv) an exploratory trial comparing added imepitoin with added potassium bromide in dogs resistant to treatment with phenobarbital or primidone.^{31,32,35,45,46} Overall, >400 dogs were treated in these trials, and each study identified consistent anticonvulsant efficacy for imepitoin.⁴⁵

Levetiracetam

Levetiracetam was approved by the FDA in 1999 for treatment of refractory focal onset seizures in adults. The drug possesses several favorable pharmacokinetic properties in dogs, including rapid, complete absorption after PO administration, minimal protein-binding,⁴⁷ lack of hepatic metabolism with the drug primarily excreted unchanged in the urine,⁴⁸ and a wide safety margin (ie, high therapeutic index). Levetiracetam is rapidly metabolized, with an elimination half-life between 4 and 8 hours.⁴⁷ As such, levetiracetam has gained considerable popularity in veterinary medicine. However, there currently are no published reports evaluating the use of levetiracetam as first-line treatment in dogs with epilepsy.

Zonisamide

Information on the clinical efficacy of zonisamide in epileptic dogs is limited to 3 small open-label, uncontrolled studies, with only a single monotherapy study.^{49–51} The only study on the use of zonisamide as monotherapy for canine idiopathic epilepsy included 10 dogs with generalized-onset seizures receiving zonisamide at 5–15 mg/kg PO q12h to achieve serum zonisamide concentrations of 10–40 µg/mL.⁵¹ Of these dogs, 60% (6/10) had a ≥ 50% decrease in monthly frequency of seizures with a follow-up of 12–36 months. The mean zonisamide dosage in these 6 dogs was 7.92 ± 3.79 mg/kg q12h. The remaining 4 dogs had an unsatisfactory response of unchanged or increased seizure frequency in 2 dogs each, respectively. Mean peak (3 hours after PO administration) zonisamide serum concentrations were 15.24 ± 5.95 µg/mL (range, 7.7–24 µg/mL) in the 6 dogs with favorable response and 22.41 ± 19.69 µg/mL (range, 9.3–51.6 µg/mL) in the 4 dogs with an unsatisfactory response.⁵¹

How Should Monitoring Be Performed?

The objectives of monitoring trough serum concentrations of any AED are to: (i) Determine effective drug concentrations after initiation of successful treatment (as appropriate); (ii) Determine if drug failure is because of pharmacokinetic factors so as to focus on a change in dose (metabolic tolerance) or pharmacodynamic factors so as to focus on a change of drugs (functional tolerance); (iii) Determine if treatment failure is caused by poor compliance or an inadequate or changed drug concentration; (iv) Prevent toxic effects; and (v) Aid with individualization of treatment.⁵²

Optimal comparison of successive drug concentrations is best achieved by evaluating concentrations

determined at the same time after dosing. Debate on the necessity of trough concentration sampling exists. Trough concentrations are best used when patients are most likely to seizure just before the next scheduled dosing for drugs with shortened elimination half-lives, and if an abnormal drug reaction is suspected.

Chronic AED use necessitates achieving a steady-state condition, in which a specific drug dose and interval result in a serum concentration that fluctuates within a reference range.⁵³ This therapeutic range is a population-based statistical concept whereby the majority of patients will seizure below the lower limit of the range and the majority of patients will have toxic effects above the upper limit of the range. Overall, the therapeutic range is best determined on an individual basis. Adjustments are based on each patient's efficacy and tolerance response. The panel recommendations are summarized in Table 2.

Phenobarbital

Serial serum phenobarbital concentrations should be evaluated at the first steady-state concentration point of 2 weeks and at the steady-state clearance time point of 6 weeks, because enhanced clearance from hepatic auto-induction can occur.²⁶ Additional monitoring at 6-month intervals thereafter, if the pet has >2 seizure events between these times, and at 2 weeks after a dosage change is recommended. Although blood concentration fluctuations may not be dramatic throughout the day in dogs with steady-state concentrations,⁵⁴ trough blood samples are best taken in the early morn-

ing, before dosing, in a fasted dog, to increase consistency in comparison with published information, maintain consistency in interpretation and avoid diurnal changes or dietary-induced fluctuations in absorption.^{55,56} Significantly lower trough compared to non-trough concentrations were reported in dogs receiving >10 mg/kg/day of phenobarbital.⁵⁷

The most efficacious and safe therapeutic range reported for dogs is 15–35 µg/mL,^{26,30,58} although efficacy can be seen at lower concentrations. Metabolic tolerance is present when progressive dose increases without concurrent parallel increase in serum drug concentration occurs, most likely because of other drugs that are p450 enzyme inducers or genetic variations. Conversely, phenobarbital will increase clearance of several other AEDs, including levetiracetam,^{59,60} zonisamide⁶¹ and clorazepate.⁶²

Bromide

Potassium bromide serum concentration measurements are recommended at the first steady-state concentration point between 6 and 12 weeks then on an annual basis or if > 3 seizures occur before the next scheduled evaluation, or if signs of toxicity are suspected. Because of the long elimination half-life, samples can be collected at any time point >2 h after dosing to avoid any peak effect variability.⁶³ The reported therapeutic range is individualized according to the high variability in patient response and tolerance to the drug. Studies have shown that bromide concentrations between 810 and 2500 µg/mL with phenobarbi-

Table 2. Qualified criteria recommendations for AED drug use.

Drug	Indications			Drug monitoring	Cautions and risks	Initial dose
	Seizure type	Seizure etiology	Other			
Phenobarbital Monotherapy Add-on	All All	All All		2 and 6 weeks, q6m, or 2 weeks after dose change; Range: 15–35 µg/mL Increases clearance of levetiracetam and zonisamide	Hepatotoxicity Idiosyncratic blood dyscrasia Necrolytic dermatitis	2.5 mg/kg q12h
Potassium Bromide Monotherapy Add-on	All All	Idiopathic All	Low initial frequency Liver disease	1 and 3 months, q12m or 1 month after dose change Range: 1000–3000 mcg/mL (mono) or 800–2500 mcg/mL with phenobarbital	Pancreatitis Sedation Ataxia	40 mg/kg/day
Imepitoin Monotherapy Add-on	All NR	Idiopathic NR		NR		15 mg/kg q12h
Levetiracetam Monotherapy Add-on	All All	All All	Liver disease	NR	Renal disease	20 mg/kg q8h
Zonisamide Monotherapy Add-on	All All	All All		2 and 3 months, q6m and 2 weeks after dose change Range: 10–40 mcg/mL	Idiosyncratic renal and hepatic disease	5 mg/kg q12h 7–10 mg/kg q12h with phenobarbital

NR = not recommended.

tal combination treatment are effective,^{34,40,64} whereas monotherapy efficacy was seen with higher concentrations up to 3000 µg/mL.^{34,64} The dosage can be adjusted according to the formula: $(\text{Target } C_{ss} - \text{Actual } C_{ss}) \times (\text{Clearance}/\text{Bioavailability}) = \text{mg/kg/day}$ added to the existing dose (where $\text{Clearance}/\text{Bioavailability} = 0.02$ and C_{ss} = steady-state concentration).

No known drug contraindications have been reported, and bromide undergoes no hepatic metabolism or protein-binding. Concomitant use of phenobarbital can enhance the risk of sedation and weakness. Clearance may be decreased in dogs with impaired renal function, resulting in higher steady-state concentrations.

Primidone

As described above, the active metabolite phenobarbital is responsible for >85% of the anticonvulsant effect obtained during treatment of dogs with primidone. Thus, primidone treatment can be monitored by plasma concentrations of phenobarbital.^{41–43,58} The therapeutic plasma concentration range of phenobarbital in dogs treated with phenobarbital or primidone is the same.³⁰

Imepitoin

Imepitoin has a relatively short half-life in dogs of approximately 2 hour so that no clinically relevant drug accumulation develops during prolonged treatment with clinically used dosages (10–30 mg/kg q12h).⁴⁵ Furthermore, interindividual differences in half-life are low, the therapeutic index is high (ie, toxicity is minimal, thus making rapid dose adjustment less likely to cause adverse effects) and the therapeutic concentration range is not known.⁴⁵ There is no indication that imepitoin alters the metabolism of other drugs, including AEDs.⁴⁵ As such, therapeutic drug monitoring is not needed for monitoring treatment and currently not commercially available.

Levetiracetam

Serum concentrations of levetiracetam are not routinely measured in clinical practice, based on the drug's wide therapeutic index and lack of an established relationship between levetiracetam concentrations and both treatment response and adverse effects in people and dogs.⁶⁵ In people, the generally accepted range is 12–46 µg/mL.⁵³ A reference range for levetiracetam has not been established in dogs, although the range in humans often is extrapolated for use in dogs.

There is evidence to support the use of levetiracetam therapeutic drug monitoring when levetiracetam and phenobarbital are used in combination. Concurrent administration of phenobarbital has been shown to alter the pharmacokinetics of levetiracetam in normal dogs as well as dogs with epilepsy, resulting in lower peak concentrations and more rapid elimination.^{60,66} Monitoring levetiracetam serum concentrations in these instances can help determine whether an increase in

levetiracetam dosage might be warranted in an effort to optimize treatment on an individual basis. No known drug-drug interactions have been reported for levetiracetam in dogs.

Zonisamide

Zonisamide is metabolized predominantly by hepatic enzyme CYP3A4, and coadministration with other medications that induce or inhibit CYP3A4 that may change zonisamide pharmacokinetics in people. Coadministration with phenobarbital (a CYP3A4 inducer) increases zonisamide clearance by approximately 50% and shortens the elimination half-life.⁶⁷ In dogs, repeated phenobarbital administration enhances CYP3A activity,⁶⁸ but the CYPs involved in zonisamide metabolism have not yet been established. It has been shown however that concurrent administration of zonisamide and phenobarbital alters zonisamide pharmacokinetics. Repeated PO administration of phenobarbital (5 mg/kg q12h for 30–35 days) decreased the bioavailability, maximum serum concentration, area under the serum concentration versus time curve, and apparent elimination half-life, and increased the total clearance of zonisamide.⁶⁹ Time to maximum serum concentration and volume of distribution were not affected by concurrent phenobarbital administration. Zonisamide pharmacokinetic parameters were restored to the same values as before phenobarbital administration 12 weeks after phenobarbital discontinuation.⁶⁹

Zonisamide does not appear to affect its own metabolism or disposition of other medications because it has not been shown to induce or inhibit hepatic CYP450 isoenzymes.⁷⁰ Zonisamide is a weak carbonic anhydrase inhibitor and therefore caution is warranted when it must be administered concurrently with other carbonic anhydrase inhibitors.⁷¹

The therapeutic target range for zonisamide of 10–40 µg/mL in people can be used as guidance regarding effective concentrations that can be targeted in dogs. Serum zonisamide concentration should be monitored 1–2 weeks after treatment initiation or dosage adjustment and any time seizure frequency increases. Currently, there are no recommendations on optimal timing of blood sampling for zonisamide concentration monitoring. In a study assessing both trough and peak serum zonisamide concentrations in 12 epileptic dogs, all but 1 trough and all peak serum zonisamide concentrations were within the target range of 10–40 µg/mL but estimated peak zonisamide concentrations were significantly higher than trough concentrations.⁴⁹ In a recent pharmacokinetic study, fluctuation between peak and trough concentrations (C_{max} and C_{min}) was 10% at steady state.⁶¹

The panel recommends collecting a trough sample within 1 hour before the next scheduled dose to allow assessment of the lowest concentration that occurs during a dosing interval and similar comparison of results of serial samples. Both trough and peak (3–4 hours after zonisamide administration) samples should be col-

lected in dogs with recurrent epileptic seizures concurrently on phenobarbital to investigate the potential role of rapid zonisamide elimination as a cause for therapeutic failure.

What Are The Risks Of Treatment?

Adverse effects can be divided into transient, persistent, and life-threatening categories (either idiosyncratic or predictable). Most transient adverse effects are avoidable with titration dosing and dissipate within several weeks. Persistent effects are either central nervous system (CNS) dose-dependent effects such as sedation, ataxia, imbalance or cognitive impairment or metabolic-related with hormonal imbalances, metabolic syndromes, and degenerative effects. Severe life-threatening effects mainly are associated with either idiosyncratic bone marrow toxicity (eg, aplastic anemia) or predictable organ damage over time (eg, hepatotoxicity).

Four categories of adverse effects were established for each drug.⁷²

Type I: Predictable and directly related to pharmacologic effects in a dose-dependent fashion

Type II: Unpredictable (idiosyncratic) and potentially life-threatening

Type III: Cumulative with long-term treatment and potentially life-threatening

Type IV: Delayed (carcinogenic or teratogenic) and life-threatening

The panel conclusions and recommendations are summarized in Tables 1 and 2.

Phenobarbital

Type I: Phenobarbital generally is well tolerated at the previously mentioned therapeutic serum concentrations in dogs. Behavioral changes, such as hyperexcitability, restlessness, or sedation, may occur after starting treatment with the drug, but they appear not to be dose-related and typically resolve within 1–2 weeks.

Type II: A more serious idiosyncratic reaction is development of immune-mediated anemia, neutropenia, thrombocytopenia, or some combination of these,⁷³ with a low prevalence of 4.2% in 1 study.⁷⁴ Typically, this reaction occurs within the first 6 months of treatment and is reversible with drug removal and appropriate treatment. Rare acute, idiosyncratic hepatotoxic reactions may occur also, as evidenced by a rapid increase of alanine aminotransferase (ALT) activity and abnormal pre- and postprandial serum bile acid concentrations. Phenobarbital also may be a risk factor for development of superficial necrolytic dermatitis in dogs.⁷⁵

Type III: Chronic adverse effects usually affect water consumption (polydipsia) and appetite (polyphagia). As a result, dogs may develop psychogenic polydipsia with associated polyuria. The most common serum biochemical change with chronic phenobarbital treatment is an increase in the serum alkaline phosphatase (ALP) activ-

ity,^{76–78} which can occur as soon as 2 weeks after initiating treatment. Neither endogenous adrenocorticotrophic hormone (ACTH) concentration nor the response to exogenous ACTH administration is altered by phenobarbital dosing.⁷⁹ Moreover, phenobarbital does not interfere with the low-dose dexamethasone suppression test, regardless of dose or treatment time.⁸⁰ Serum total and free thyroxine (T4) concentrations may be low in dogs treated with phenobarbital, resulting in a mistaken diagnosis of hypothyroidism.^{81,82}

A less common but potentially life-threatening complication is drug-induced hepatotoxicity. Documentation of a serum phenobarbital concentration >35 µg/mL had the highest correlation with the development of hepatotoxicity.⁸³ All dogs on chronic phenobarbital treatment should have a serum biochemistry profile performed every 6 months to monitor for development of chronic hepatotoxicity followed by a bile acid tolerance test if altered liver function is suspected.

Type IV: Not reported in the dog.

Bromide

Type I: Potassium bromide generally is well tolerated in the dog. The most common adverse effects seen with potassium bromide with or without phenobarbital combination treatment are polydipsia, polyphagia, increased lethargy, and mild ataxia with increasing serum bromide concentration.⁸⁴

Type II: Potassium bromide is a known mucosal irritant and capsules may result in gastric irritation because of direct contact of a concentrated amount of the drug with the gastric mucosa. Pancreatitis and gastrointestinal intolerance also have been reported.⁸⁵

Type III: Intoxication to the point of stupor is rare, but pelvic limb ataxia, weakness, and altered behavior are more likely with serum concentrations >3000 mg/l.⁸⁶ Caution should be used when treating dogs with underlying renal insufficiency because of decreased renal elimination.⁸⁷ Treatment for potassium bromide intoxication consists of IV administration normal saline to enhance renal excretion.⁸⁶ Careful monitoring is advised because dogs may become more susceptible to seizure activity with lowering of the serum bromide concentration.

Type IV: Not reported for the dog.

Primidone

Type I: Treatment with primidone is associated with adverse effects similar to those documented with phenobarbital treatment.

Type II: Treatment with primidone is associated with adverse effects similar to those documented with phenobarbital treatment.

Type III: Increased hepatic enzyme activity is more frequent and severe with primidone than with phenobarbital,^{30,77,88} which can be explained by assuming that both intact primidone and its active metabolite phenobarbital affect the liver. As a consequence, primidone is

associated with a higher frequency of hepatotoxicity than phenobarbital hepatic necrosis, fibrosis and cirrhosis all have been associated with chronic use of primidone.^{76,88,89} Therefore, liver enzyme assays and function tests should be performed every 3–6 months to monitor for toxicity in dogs.

Type IV: Not reported in the dog.

Imepitoin

Type I: In a safety study under laboratory conditions, healthy Beagle dogs were given 0, 30, 90, or 150 mg/kg imepitoin PO q12h for 26 weeks.³⁵ Complete safety evaluation including histopathology was performed. A no-observed-adverse-event dosage of 90 mg/kg PO q12h was obtained, well above the recommended doses for clinical use of 10–30 mg/kg PO q12h.^{44,46} In clinical studies in epileptic dogs, treatment with imepitoin was associated with relatively mild adverse effects in part of the animals, including somnolence, sedation, transient polyphagia, polyuria, polydipsia, and hyperactivity.^{35,90} Except hyperactivity, all these adverse effects were less frequent than with phenobarbital.³⁵

Type II: Not reported in the dog.

Type III: No significant alterations in liver enzyme activity were observed with imepitoin.³⁵ Studies in healthy dogs indicated that chronic treatment with imepitoin should not lead to development of tolerance or dependence, and that abrupt termination of treatment should not result in severe withdrawal effects, including seizures and status epilepticus.^{31,44}

Type IV: The safety profile of imepitoin was further characterized *in vitro* using genotoxicity assays, and in mice, rats, and dogs with multiple dosing.^{35,44} Imepitoin was shown to not be genotoxic, teratogenic, or immunotoxic.

Levetiracetam

Type I: All of the reported adverse effects associated with levetiracetam administration in dogs are predictable and related to its pharmacologic effects in a dose-dependent fashion. Preclinical studies performed on healthy dogs by the drug manufacturer described unsteady gait, salivation, vomiting, and sedation with repeated PO dosing at 300–1200 mg/kg/day (5–20 times the recommended dosage for dogs).⁹¹ Clinical studies evaluating the use of levetiracetam as supplemental treatment in dogs with epilepsy indicated that the drug was well tolerated, with infrequent reports of adverse effects.^{92,93} Sedation, ataxia, restlessness, vomiting, and decreased appetite have been described, although ataxia was the only effect shown to differ significantly from baseline in a randomized, controlled study involving 34 dogs.⁹³

Type II, III, and IV: Not reported in the dog.

Zonisamide

Type I: The reported adverse effects of zonisamide include sedation, generalized ataxia, vomiting, and inappetence.^{50–52} The prevalence of these adverse effects

varied among studies from 10% (1/10 dogs)⁵¹ to 55% (6/11 dogs)⁵⁰ Although in some dogs ataxia and sedation were transient and required no dosage change, in other individuals a dose reduction was necessary.^{50,51,5010} Sedation, vomiting, and inappetence resolved in 1 dog after discontinuation of zonisamide.⁵¹ As in humans, gradual titration to final maintenance dosage may help decrease the frequency and severity of these adverse effects.

Type II: Idiosyncratic reactions to zonisamide are rare in dogs. As in people, patients with a previous allergic episode to sulfonamide-containing medications are at higher risk for developing such reactions.⁶⁷ Keratoconjunctivitis sicca and polyarthropathy (both of which may be potential adverse effects of sulfonamide-based medications) were reported in 1 dog each but a clear cause and effect relationship with zonisamide administration could not be proven.⁹⁴

Suspected life-threatening idiosyncratic adverse effects of zonisamide in dogs include acute toxic hepatopathy reported in 2 dogs^{95,96} and renal tubular acidosis reported in 1 dog.⁹⁷ Discontinuation of zonisamide resulted in clinical improvement in 2 of 3 dogs, with 1 dying as a result of hepatopathy.

On the basis of these reports, hepatic enzyme activity, electrolytes, blood gas analysis, and hematology should be assessed before initiation of zonisamide and monitored periodically during zonisamide treatment. An increase in serum chloride concentration and a decrease in bicarbonate or TCO₂ should prompt further investigation of renal tubular acidosis.⁹⁷

Type III: Zonisamide treatment may affect thyroid function and some clinical laboratory test results. In a pharmacokinetic study of healthy dogs given zonisamide at 10.3 mg/kg PO q12h for 8 weeks, mean serum total T4 concentration decreased below the normal reference range but mean free serum T4 and TSH concentrations were within the reference range after 6 months of treatment. Increases in serum ALP activity and serum calcium concentration and decreases in serum total protein and albumin concentrations were reported compared to baseline but remained within reference range.⁶¹ A small but statistically significant decrease in serum albumin concentration and an increase in ALP activity have been reported in research dogs given zonisamide at a dosage of 75 mg/kg/day for 52 weeks.⁹⁸ These studies demonstrate the potential for zonisamide to cause hepatotoxicity.

Type IV: Not reported in the dog.

When Should a Second AED Be Started and Which Should be Used?

Epilepsy treatment should be goal-oriented and approached in an objective fashion. The decision to add a second AED is based on seizure frequency, severity (duration, cluster activity, postictal effects), and overall quality of life. Risk factors associated with poorer seizure control include male dogs and prior cluster seizure activity.⁹⁹ Strict criteria for decision-making strategy on starting a second AED are lacking in veterinary medicine. Several factors should be considered when deciding on a

second AED. Selection of an AED with a different mechanism of action, minimizing drug-drug interactions, avoiding additive toxicity, and determination of risk-benefit of polypharmacy versus quality of life are all important considerations. A discussion on drug resistance is provided in a supplementary file. The panel conclusions and recommendations are summarized in Table 1.

Phenobarbital

With phenobarbital being used predominantly as a first-line AED in dogs, no studies on its use as a supplemental treatment were identified. However, phenobarbital has been used extensively in combination with several AEDs, as noted below. Phenobarbital has important drug-drug interactions with drugs metabolized by the liver that can influence drug concentrations.

Bromide

Concomitant potassium bromide and phenobarbital administration decreased seizure number and severity in the majority of dogs in several studies, with seizure-free status ranging from 21% to 72% of all treated dogs.^{39,40,64} These studies, however, were noted to carry a higher degree of bias.⁸ By allowing a decrease in the use of drugs metabolized by the liver, potassium bromide treatment also may decrease the frequency of hepatotoxicity.

Primidone

Because primidone has no advantage in efficacy compared to phenobarbital but is associated with a higher risk potential, especially hepatotoxicity, it should not be used as a second or alternative drug in dogs in which monotherapy with phenobarbital, imepitoin, or other first-line drugs failed. In epileptic dogs that do not respond to monotherapy with primidone, potassium bromide has been added, but with only limited therapeutic success.^{31,32}

Imepitoin

There is only very limited published information on supplemental treatment with imepitoin. In a prospective trial in 17 dogs with chronic epilepsy, in which imepitoin was added to the current treatment with phenobarbital or primidone, most dogs exhibited decreases in seizure frequency and severity, and imepitoin was better tolerated than potassium bromide when used as supplemental treatment.^{31,32} Furthermore, the supplemental treatment with imepitoin (10–15 mg/kg PO q 12 h) did not appear to aggravate the CNS-related adverse effects of phenobarbital or primidone.³²

Levetiracetam

To date, all of the published studies on levetiracetam for dogs with epilepsy have evaluated its use as supplemental treatment in dogs refractory to phenobarbital,

bromide, or both. A research abstract described retrospective evaluation of 15 dogs with long-standing generalized seizures that were treated with levetiracetam at PO dosages of 7.1–23.8 mg/kg q8h as part of their AED regimen.¹⁰⁰ A 54% decrease in seizure frequency over 3 months compared to baseline was reported.

An open-label, prospective, non-comparative trial of levetiracetam was performed in 14 dogs with idiopathic epilepsy resistant to phenobarbital and bromide.⁹² Diagnosis of idiopathic epilepsy was based on normal interictal neurologic examination, exclusion of metabolic causes, and normal MRI and CSF findings. Levetiracetam initially was administered PO at a dosage of 10 mg/kg PO q8h for 2 months with dose escalation to 20 mg/kg PO q8h for 2 months in dogs that experienced a decrease in seizure frequency of <50% from baseline with no major adverse effects. Nine of 14 (64%) dogs were reported to be ‘responders’, with a decrease in seizure frequency of > 50%. In the population as a whole, a significant decrease in the overall monthly seizure frequency of 55% and a decrease in seizure days per month of 43% were observed. However, 6 of 9 (67%) responders experienced an increase in seizure frequency and seizure days per month after 4–8 months of continuing treatment at the last effective levetiracetam dose.

A randomized, double-blinded, placebo-controlled cross-over study evaluated 34 dogs refractory to phenobarbital and bromide.⁹³ Diagnosis of idiopathic epilepsy was based on compatible signalment and history, normal physical and neurologic examinations, and exclusion of metabolic causes. Advanced imaging and CSF analysis were not required for participation in the study. After a prospective baseline period of 8 weeks, dogs were randomized to receive either oral levetiracetam (20 mg/kg PO q8h) or matching placebo for 16 weeks. After a 4-week wash-out period, dogs received the alternate treatment for an additional 16 weeks. As a consequence of a high dropout rate (35%), comparisons were made between the dogs receiving levetiracetam during the first treatment (n = 18) and those receiving placebo during the first treatment (n = 10). Although a significant decrease in weekly seizure frequency compared to baseline was identified for dogs receiving levetiracetam, the reduction in seizures was not significant when compared to placebo. There was no statistical difference in the number of dogs classified as responders with levetiracetam administration (56%) compared to placebo (30%).

A retrospective evaluation of dogs treated at an epilepsy referral center described response rates to successively administered antiepileptic drugs.¹⁰¹ In this study, 32 dogs were given a third-line drug after failure to respond to phenobarbital and bromide in combination, 27 of which were treated with levetiracetam. Over one-third (38.5%) of dogs responded to the third-line drug, with a 50% or greater decrease in seizure frequency, but none of the treated dogs became seizure-free. However, it was not specified how many of these responders were being treated with levetiracetam versus another third-line drug.

Zonisamide

Overall, the efficacy of zonisamide to decrease seizure frequency by $\geq 50\%$ in 23 epileptic dogs with generalized seizures has been reported to be 58–80% when used as an adjunctive antiepileptic medication.^{49,50} The 80% efficacy refers to the first 4 months of zonisamide treatment.⁵⁰ An open-label, noncomparative study including 12 idiopathic epileptic dogs poorly controlled with phenobarbital alone or in combination with bromide or other AEDs or both and given zonisamide at a mean dosage of 8.9 mg/kg q12h, reported a median decrease in seizure frequency (when comparing ≥ 8 weeks before and after treatment initiation) of 84.5% (range, 54.8–100%; mean, 81.3%) in 7 (58%) dogs.⁴⁹ Two of these 7 dogs became seizure-free. Concurrently administered AEDs including phenobarbital, bromide, felbamate, or clorazepate could be decreased in dosage or discontinued in all 7 responders to zonisamide. The mean decrease in phenobarbital dosage was 92.2%. The remaining 5 dogs (42%) experienced a median increase in seizure frequency of 52.6% (range 7.4–100%). All 12 dogs in this study experienced generalized seizures, and 2 of them also had focal seizures.⁴⁹ The mean and median follow-up times after zonisamide administration were 33.5 weeks and 37 weeks, respectively (range, 8–71 weeks). In all dogs, the PO dosage of zonisamide was adjusted to achieve serum concentrations between 10 and 40 $\mu\text{g/mL}$. There were no significant differences between serum zonisamide concentrations in responders versus nonresponders for either trough or peak concentrations.⁴⁹

Another open-label, non-comparative study included 11 idiopathic epileptic dogs with generalized seizures poorly responsive to phenobarbital, bromide, or both and treated with zonisamide at a dosage of 10 mg/kg.⁵⁰ Zonisamide was administered as adjunctive treatment in 10 dogs and as monotherapy in 1 dog that developed phenobarbital-induced hematologic abnormalities. Seizure frequency during the 4 months before and after zonisamide treatment was compared. Eight of the 10 dogs (80%) given zonisamide as adjunctive treatment had a median decrease in seizure frequency of 82.7% (range, 58–100%) during the 4 months after zonisamide treatment was initiated. However, seizure frequency increased in 3 of these 8 dogs after long-term follow-up (7–17 months). The dog on zonisamide monotherapy experienced a seizure reduction of 100% with a 17-month follow-up. The remaining 2 dogs included in the study had seizure reductions of 14% and 25%, respectively. Seizure duration and severity (eg, single seizures instead of cluster seizures or status epilepticus) decreased in 2 dogs. The dose of phenobarbital, bromide or both could be decreased in 7 dogs without subsequent impairment of seizure control.⁵⁰

What Alternative Nonpharmacologic Treatments Are Available?

Vagal Nerve Stimulation

Vagal nerve stimulation (VNS) involves surgical implantation of a pacemaker-like device that delivers

repetitive electrical stimulation to the left cervical vagus nerve and is now approved for use in people of all ages and seizure types. The mechanism by which VNS exerts its antiepileptic effect is not completely understood, but it is believed that stimulation of afferent vagal fibers influences brain activity by modulation of noradrenergic and cholinergic synaptic transmission in people^{102,103} and dogs.¹⁰⁴ Approximately, half of humans treated with VNS will experience a positive response, with a $> 50\%$ decrease in seizure frequency with a positive correlation with efficacy with duration of treatment.¹⁰⁵

Preclinical studies evaluating VNS as a treatment for seizures performed in normal animals first demonstrated that intermittent stimulation of the left cervical vagus trunk could effectively prevent experimentally induced seizures in dogs.¹⁰⁶ A randomized, placebo-controlled, crossover study evaluating the use of VNS in 10 dogs with medically refractory idiopathic epilepsy found no significant difference in seizure frequency, severity, or duration between treatment and control groups over the course of the 12-week study, but a 34% significant decrease in seizure frequency was observed in the last 4 weeks of treatment.¹⁰⁷

Dietary Alteration Treatment

The most well-known dietary treatment for human epilepsy is the ketogenic diet, which is a high fat, low protein, low carbohydrate diet designed to mimic the biochemical changes of fasting to potentiate mitochondrial-dependent energy metabolism in neurons and inhibition of glutamatergic metabolic pathways and synaptic transmission.^{108,109} A randomized, double-blinded, controlled trial evaluated the effectiveness of a high-fat, low-carbohydrate diet compared to controls for seizures in dogs with drug-resistant idiopathic epilepsy.¹¹⁰ The study failed to identify a difference in seizure frequency between the groups and 3 of 9 dogs fed the ketogenic diet developed pancreatitis. In contrast, a medium chain triglyceride (MCT)-based diet developed for the treatment of cognitive dysfunction in dogs¹¹¹ was evaluated in dogs with idiopathic epilepsy, a 6-month prospective, randomized, double-blinded, placebo-controlled crossover dietary trial.¹¹² Seizure frequency and monthly seizure days were significantly lower in the 21 dogs finishing the trial when on the test diet for 12 weeks as compared to those on the placebo diet.

A recent, randomized, single-blinded, controlled crossover trial evaluated the effects of omega-3 fatty acid supplementation in 15 dogs with idiopathic epilepsy and did not identify any difference in seizure frequency or severity between the treatment and placebo groups.¹¹³

Acupuncture

A recent evidence-based assessment of published randomized controlled trials concluded that the current available information does not support the use of acupuncture in the treatment of epilepsy in people.¹¹⁴ Gold bead implants in 5 dogs with drug-resistant epi-

lepsy for 6 months identified initial seizure frequency improvement in all dogs but relapse of seizures in 2 dogs.¹¹⁵ An uncontrolled study with minimal study design details of 40 dogs with idiopathic epilepsy reported that 50% of dogs could be taken off all medication after receiving gold bead implantation, with 20 dogs having recurrent epileptic seizures, 10 dogs treated with decreased AED dosage, and 10 dogs having no response. A controlled open-label study evaluating 7 drug-naïve and 8 AED-treated dogs before and after gold bead implants¹¹⁶ reported a 38.7% decrease in mean seizure frequency for all dogs. No change in EEG recordings in acupuncture-treated dogs was reported.¹¹⁷

Homeopathy

Homeopathic remedies most frequently used in humans with epilepsy include silicea, cuprum, causticum, hyosciamus, *Aethus cynapium*, *Agaricus muscarius*, *Absinthium*, *Artemisia absinthium*, *stramonium*, and *Cicuta virosa*. Evidence to support the use of these treatments currently is lacking.^{118,119}

What are the Guidelines for Success and Quality of Life Parameters?

The most important outcome measure of a chronic medical condition such as epilepsy is quality of life (QOL). For dogs, QOL is reflected not only by the degree of therapeutic success but also by maintaining a high QoL while living with epilepsy. The determination of QoL is heavily influenced by the burden placed on the household members as owners. Owners will choose euthanasia if the emotional stress, psychosocial challenges, economic burden, or some combination of these associated with having an epileptic dog in the household exceeds the expectations of the owner. Dogs with epilepsy have been reported to have an increased risk of premature death as a result of euthanasia.^{1,120,121} Several factors may influence therapeutic success, in particular seizure etiology. A recent study investigating dogs with idiopathic and structural epilepsy separately, found that the median life span for dogs with idiopathic epilepsy was not decreased when compared with the median life span of dogs in general, whereas the median life span for dogs with structural epilepsy was significantly reduced.¹²² The poor prognosis of structural epilepsy reflects its etiology in which epileptic seizures are provoked by confirmed intracranial cerebral pathology. Breed also may influence outcome because certain breeds (eg, Labrador retriever, Belgian shepherd) experience mild epilepsy with good outcome,^{123,124} whereas other breeds (eg, Border collie, Australian shepherd) suffer from a more aggressive form of epilepsy, and may experience a more unfavorable outcome.^{125,126} Furthermore, the tendency to develop cluster seizures or status epilepticus has been found to negatively influence outcome in dogs with epilepsy.^{127,128}

Overall, the owners' perspectives regarding the overall impact of epilepsy on the household will determine if the epileptic dog will survive with epilepsy or not. Quality of

life of epileptic dogs and the epilepsy burden on the household have been investigated in a few studies,^{1,2,129} but these are difficult to assess objectively because owner-based questionnaires addressing issues that will influence a potential decision of euthanasia form the basis of such investigations. To date, no standardized validated QOL questionnaires exist for dogs with epilepsy.

Measures of the epilepsy burden on families should include questions regarding restrictions on the owner's and household's life, and frustrations over caring for a dog with epilepsy, as well as emotional stress and anxiety experienced in the household. Ultimately, economic considerations and intrahousehold disagreements regarding QOL of living with an epileptic dog factor heavily in the decision to euthanize. The goal is to aid owners in the decision-making process on QOL as it pertains to themselves and their epileptic pets.

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Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

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Supporting Information

Additional Supporting Information may be found online in Supporting Information:

Data S1. What is drug-resistant epilepsy?