



Newer Drugs for the Treatment of Epilepsy

Robin Levitski-Osgood, DVM, DipACVIM (Neurology)
Veterinary Specialty Hospital

The number of antiepileptic drugs (AED) available to veterinarians has increased over the past few years. These drugs fit into three broad categories based on their mechanism of action.

1. Enhancement of inhibitory processes via GABA
2. Reduction of excitatory transmission
 - 3a. Modulation of membrane conductance of Na⁺ channel
 - 3b. Modulation of membrane conductance of Ca²⁺ channel

Previously the most commonly used AEDs fit into the same mechanism category of enhancing inhibition in the brain (phenobarbital, potassium bromide, and benzodiazepines). Now we have a broader selection of drugs that have other mechanisms of action in addition to the enhancement of inhibitory processes. Our primary limitations with AEDs are toxicity, tolerance, poor pharmacokinetics, and financial expense. We are unable to use many of the AEDs used in people for our patients due to the short half lives and the potential for hepatotoxicity.

Potassium bromide is my first choice in most dogs that have been diagnosed with idiopathic epilepsy and are having intermittent seizures. Phenobarbital is my first choice in dogs with frequent severe seizures, status epilepticus, and epilepsy due to structural brain disease (brain tumors, masses, infectious or inflammatory disease).

Newer 3rd line anticonvulsants MOA

Felbamate (Felbatol®): (1, 2, 3a)

Gabapentin (Neurontin®): (1, 2, 3a, 3b)

Levetiracetam (Keppra®): (1, 2, 3b)

Topiramate (Topamax®): (1, 2, 3a)

Zonisamide (Zonegran®): (3a, 3b)

Felbamate (Felbatol®): In people it is most useful in the treatment of uncontrolled partial epilepsy. It has been documented to control focal seizure activity in the dog. Side effects in people include idiosyncratic aplastic anemia and liver toxicity. Blood cytopenias and hepatotoxicity in the dog have not been published in the literature (that I could find). Sedation is not a typical side effect. Serial monitoring of the CBC and chemistry panel is recommended at 1 month and then q 3-6 months during therapy.

\$200.00/month to treat a 50 lb/22 kg dog

Dosage: 15-20 mg/kg TID (up to 65 mg/kg/day)

Gabapentin (Neurontin®): In people it is most useful as an add-on therapy to treat refractory partial and generalized seizures. Sedation and ataxia are possible side effects in the dog. Dosing may need to be TID (or even QID) due to the rapid elimination of the drug. Can start with the lower end of the dose and work up to the higher end of the range.

\$120.00/month to treat a 50 lb/22 kg dog

Dosage: 10-30 mg/kg BID to TID

Levetiracetam (Keppra®): Very well tolerated drug in human clinical trials. Adverse effects in people were equal to the placebo side effects. In people it has been highly effective as an adjunctive medication to control partial seizures that were previously refractory to treatment. There are no specific side effects reported in the dog. Can start with the lower end of the dose and work your way up.

\$130.00/month to treat a 50#/22kg dog. Oral solution

\$115.00/month for the tablets

Dosage: 10-20 mg/kg BID to TID

Topiramate (Topamax®): In people it has been used for many seizure types in both adult and pediatric patients. Side effects in dogs include GI upset, anorexia and irritability. Another one that can be started at the low end of the dose and gradually increased.

\$315.00/month to treat a 50#/22kg dog.

Dosage: 2-10 mg/kg BID

Zonisamide (Zonegran®): In people it has been used for a variety of seizure types and particularly adult myoclonus epilepsy. Major side effects in people include a higher incidence of renal calculi, sedation, and GI disorders. Side effects in the dog include sedation, ataxia, and anorexia. This drug is a sulfonamide so keep in mind hypersensitivity reactions.

\$200.00/month to treat a 50#/22 kg dog.

Dosage: 5-10 mg/kg BID

Drugs to consider for future use:

Stiripentol: Used for severe myoclonic epilepsy of infants. Also used in combination with carbamazepine for refractory partial epilepsy in children. It is structurally unrelated to any other antiepileptic medication. There are no dose recommendations available for the dog at this time.

ELB138: Not available yet. This new drug has recently been evaluated in a pilot study with 29 dogs with epilepsy. Initial data is very promising. The reduction in seizure frequency in newly diagnosed epileptics was comparable to the reduction in dogs treated with phenobarbital. Add on therapy with ELB138 in chronic epileptic patients reduced the seizure frequency and duration and severity of seizures. A multicenter blinded study needs to be done. Side effects are rare and consist mostly of transient polyphagia.

Dosage: 20 mg/kg BID

Mechanism of Action of Antiepileptic Drugs

AED	1.Enhanced GABA activated Cl ⁻ conductance (decrease sz onset)	2. Reduced glutamate mediated excitation (decrease sz spread)	3a.Enhanced Na channel inactivation (decrease sz onset)	3b.Reduced current through Ca channels (decrease sz spread)
Felbamate	X	XX	X	
Gabapentin	XX	X	X	X
Levetiracetam	XX	X		X
Topiramate	X	X	X	
Zonisamide			X	XX
Phenobarbital	XX	X		X
Bromide	XX			
Benzodiazepines	XX			

Summarized from Dr. Podell's lecture at ACVIM 2006