Rx SOLUTIONS
PEER REVIEWED

Which Drugs Control Seizures in Dogs & Cats?

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First-Line Anticonvulsants

Phenobarbital

Phenobarbital is a barbiturate primarily used as a sedative hypnotic as well as an anticonvulsant when given in subhypnotic doses.

Initial dose → 2 mg/kg PO q12h titrated to effect[1-5]

IV loading dose if needed →16–20 mg/kg total dose divided, followed by PO maintenance dose 12 hours later [1-5]
- Steady state reached by 2 weeks[1-5]

Emergency dose if needed for status epilepticus → 4 mg/kg IV

Therapeutic blood concentration → 15–35 µg/mL
- A therapeutic range of 10–40 or 15–45 µg/mL is typically cited.[1-3,6,7]
- A trough level is ideal, but one study showed that time of collection did not significantly alter the treatment plan in 91% of patients.[8]

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Key Points

- Barbiturates inhibit release of acetylcholine, norepinephrine, and glutamate and are GABA-mimetic.[1-3]
- Transient sedation and lethargy, weakness, and ataxia can be common after starting or increasing a dose.[1-5,9,10]
- Long-term PU/PD, polyphagia, and weight gain have been reported.[1-5]
- Uncommon to rare adverse events
  - Hepatotoxicity: Idiosyncratic reaction or chronic serum concentrations >35 µg/mL; although clinically significant hepatotoxicity is rare, liver enzyme induction and hepatic pathologic changes are common.[1-7,10,11]
  - Overt hepatic failure can occur with chronic administration in dogs.
  - Idiosyncratic blood dyscrasias: Anemia, thrombocytopenia, and neutropenia[2,12,13]
  - Superficial necrolytic dermatitis[14]
- Recommended testing q6mo: CBC, liver chemistry panel, bile acid testing, phenobarbital blood level[1]
- Phenobarbital may lower total thyroxine (TT_4) and free thyroxine (FT_4) and elevate thyroid stimulating hormone (TSH).
  - It is unclear if phenobarbital causes clinically significant hypothyroidism, as many patients do not show outward clinical signs of hypothyroidism.
  - Supplementation should be considered, however, if typical signs of hypothyroidism are present.[15-17]

Bromide

Bromide is often considered the first-line choice for dogs with seizures because it has no effect on the liver or as a second-line choice along with phenobarbital.[18-20]

The author prefers liquid potassium bromide (KBr), as it allows easier titration than compounded capsules or commercial chewable formulations.

Potassium Bromide

Initial dose → 20 mg/kg PO q12–24h titrated to effect[1-3,18]

- Dividing daily dose to twice-daily and mixing with food can lessen the likelihood of nausea or vomiting (do not squirt mixture directly into the mouth).

Loading dose → 400–600 mg/kg total dose divided over 1–4 days may be indicated if seizures are frequent.[1-3]

- Steady state reached at 3–4 months in dogs and 6–8 weeks in cats[1,2]
- One report described loading KBr intrarectally,[21] but it can cause discomfort and diarrhea (personal observation).

Therapeutic blood concentration → 1–3 mg/mL[1-2]

Sodium Bromide

Initial dose → To obtain NaBr dose, calculate KBr dose and reduce by 15%.[1,18]

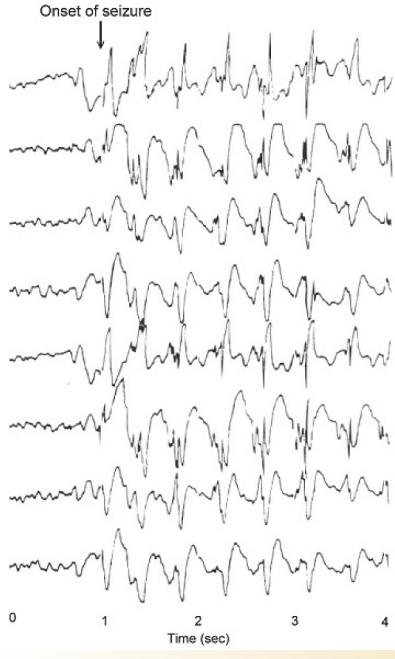
- NaBr reportedly causes less gastritis.[1]

Loading dose → Same as for KBr

Therapeutic blood concentration → Same as for KBr

Key Points

- Bromide competes with chloride transport across nerve cell membrane leading to hyperpolarization, thereby raising seizure threshold to decrease epileptic discharges.[1-3,18-20]
- Unlike phenobarbital, bromide is eliminated unchanged by the kidneys.[1,3]
- Transient (2–3 weeks) sedation/lethargy, weakness, and ataxia can be common after starting or increasing a dose.[1-3,18-20,22]
- Long-term effects include PU/PD, polyphagia, and weight gain.[1-3,18-20]
- Dietary measures: Avoid salty (high-chloride) foods, and keep salt (chloride) content steady.[23]
- **Cats only:** Up to 40% may develop eosinophilic pneumonitis; usually reversible but may cause sufficiently severe cough to necessitate euthanasia decision by owner[24,25]
- Recommended testing: CBC, serum chemistry panel, urinalysis
  - Annually for young to middle-aged dogs and cats
  - q6mo for geriatric dogs and cats
  - Hyperchloremia is a frequent observation; many laboratory analyzers cannot differentiate serum bromide from chloride, leading to falsely elevated serum chloride levels.



GABA = gamma-aminobutyric acid

From Third- to First-Line Anticonvulsants

Zonisamide

Zonisamide has traditionally been a third-line anticonvulsant but has been used more often as a first-line selection since introduction of a generic formulation.[26-28]

Dose → 5–10 mg/kg PO q12h[1,29]
- Steady state reached by 1 week

Therapeutic blood concentration → Serum concentration not routinely measured but suggested therapeutic range of 10–40 µg/mL based on limited pharmacokinetic studies[27]

Key Points

- Zonisamide is partially metabolized by the liver.[1,29,30]
- Although the mechanism of action for zonisamide is unclear, it may block sodium channels to stabilize neuronal membranes and suppress neuronal hypersynchronization.[29,30]
- Reported side effects are usually mild and include sedation, ataxia, and decreased appetite.[27,29]
- **Caution/Warning**
  - Zonisamide (a sulfonamide) should *not* be used in patients allergic to sulfa drugs.

Zonisamide and levetiracetam have traditionally been third-line anticonvulsants but are becoming more popular as first-line options since introduction of generic formulations.

Levetiracetam

Levetiracetam is typically a third-line anticonvulsant but has been used more commonly as a first-line medication (especially in patients with hepatic encephalopathy [eg, portosystemic shunt]) since a generic formulation became available.[1,29,31,32]

Dose → 10–20 mg/kg PO q8h[1,31]
- Steady state reached by 1 week

Emergency dose if needed for status epilepticus → 16–20 mg/kg total dose divided[33]

Therapeutic blood concentration → Not routinely measured

Key Points

- Levetiracetam is not metabolized by the liver but is metabolized in serum (70%) and organs other than the liver.[31,32,34]
- Mechanism of action is unclear but may prevent hypersynchronization of epileptiform burst-firing and propagation of seizure activity.[1]
- Side effects typically are mild and include sedation in dogs and lethargy and decreased appetite in cats.[1,29,31]

Felbamate

Second- or Third-Line Anticonvulsants

Felbamate is primarily used as a second- or third-line anticonvulsant *in dogs only*.[1,35,36]

Dose → 15 mg/kg PO q8h (dogs only); can increase by 15 mg/kg q2wk until maximum dose of 70 mg/kg PO q8h[1,36]

Key Points

- Mechanism of action is unclear but may activate sodium channels, thereby decreasing sustained high-frequency firing of action potentials.[1,36,37]
- Felbamate is metabolized by the liver and excreted both unchanged and as metabolites in the urine.[1,37]
- Liver enzyme induction can lead to decreased half-life.[1]
- Felbamate has increased risk for hepatotoxicity, especially when administered with other liver-metabolized medications (eg, phenobarbital).[1,29,38]
- Adverse events include liver enzyme induction, tremors, salivation, restlessness and agitation (usually at higher doses), and keratoconjunctivitis sicca (KCS; dry eye).[1,35,36]
- Blood dyscrasias (leukopenia, lymphopenia, thrombocytopenia) have been reported; sedation and nausea/vomiting also have been reported.[1-3,31,35,39]
- Recommended testing: CBC, serum chemistry panel q6mo

Gabapentin

Third-Line Anticonvulsants & Pulse Protocols

Gabapentin (Neurontin, pfizer.com) is typically a third-line anticonvulsant but is also given as a pulse protocol (in addition to daily maintenance anticonvulsants) to patients with known cluster seizures.[1,2,31,40,41]

Dose → 10–20 mg/kg PO q8–12h (dogs/cats)[1,2,31,40,41]

- Steady state reached within 1–2 days

At-home cluster protocol → 20 mg/kg PO q8h for 3 days[42]

Therapeutic blood concentration → serum concentrations not routinely measured

Key Points

- Gabapentin appears to inhibit voltage-gated calcium channels.[1,43]
- It is partially metabolized by the liver.[1,43-45]
- Side effects include sedation and ataxia.[1,2,40,41]

Clorazepate

Clorazepate is a long-lasting benzodiazepine used as a third-line anticonvulsant that also is occasionally used as a pulse protocol for cluster seizures.

Dose → 1–2 mg/kg PO q8–12h (dogs), 3.75–7.5 mg total dose q12–24h (cats)[1,29,46,47]

- Peak plasma concentrations occur in 1–2 hours.[48,49]
- Evaluation of nordiazepam (active metabolite) levels is recommended at 10 days, 30 days, and q6mo, although they are not commonly measured in veterinary neurology.[36]

Nonemergency use of oral diazepam is for cats only and is not recommended for dogs; however, the IV formulation is for emergency use in both dogs and cats.

Key Points

- Mechanism of action is unknown but may involve serotonin antagonism, increased release-facilitation of GABA activity, and decreased release/turnover of acetylcholine in the CNS.[1]
- It is metabolized by the liver to nordiazepam, which has a very long half-life (up to 100 hours in humans).[48]
- Clorazepate interferes with phenobarbital metabolism, leading to increased phenobarbital concentrations.[1]
- Most common side effects are sedation and ataxia.[1]
- Patients may develop tolerance to oral clorazepate over time.[50,51]
- **Cats only:** There is potential for hepatic necrosis.[1,36]

Diazepam

Nonemergency use of oral diazepam is for *cats only* and is not recommended for dogs, as they can develop tolerance to the oral formulation.[49]

The IV formulation is for emergency use in both dogs and cats.

Dose → 0.25–0.5 mg/kg PO q8–12h (cats); *do not use PO in dogs*[1-5,36]

For emergency → 0.5–1 mg/kg IV or 1–2 mg/kg per rectum[1-5,52]

Key Points

- Mechanism of action is unknown but may involve serotonin antagonism, increased release/facilitation of GABA activity, and decreased release/turnover of acetylcholine in the CNS.[1]
- Diazepam is metabolized by the liver into several active metabolites, including nordiazepam, oxazepam, and temazepam.[1,29]
- Fatal hepatic necrosis has only been reported with oral diazepam in cats.[53,54]
- Adverse effects include sedation, ataxia, increased appetite, and hyperexcitability.[55]
- Diazepam may (rarely) cause aggression; use with extreme caution in patients with known aggression.[55]

- **Caution/Warning**
  - Recommended testing: In cats, liver enzymes and bile acids should be monitored before and closely after diazepam therapy begins; cats may develop hepatic necrosis, which may be fatal.[1,5]

Topiramate

Topiramate is often used as a fourth- or fifth-line (add-on) anticonvulsant for *dogs only*.

Dose → 5–10 mg/kg PO q12h (dogs)[56,57]

- Topiramate has a very short half-life, 2–4 hours; but it may have prolonged clinical activity due to high-affinity binding to receptors.[56-58]

Key Points

- Mechanism of action is unknown but possibly has 3 actions:[1]
  - Blocking repetitive action potentials in neurons with sustained depolarization
  - Increasing GABA frequency of activating its receptors
  - Antagonizing kainate/AMPA receptors
- Side effects are typically mild, with sedation, weakness, ataxia, and weight loss being most common.[57,58]

Do Not Use

Anticonvulsants Warning

Several anticonvulsants used for humans should *not* be used in dogs and cats. Most have an elimination half-life that is too short to allow convenient dosing by pet owners.

- Phenytoin
- Carbamazepine
- Valproic acid
- Ethosuximide
- Lamotrigine (metabolite is cardiotoxic in dogs)

Primidone

No Longer Recommended

Primidone is no longer recommended in dogs. It is metabolized by the liver into phenobarbital and PEMA, both of which are active anticonvulsants.

There are no apparent benefits of using primidone over phenobarbital alone, and primidone may be more hepatotoxic than phenobarbital.[9,29]

AMPA receptor = non–NMDA (*N*-methyl-D-aspartate)-type ionotropic transmembrane receptor for glutamate, GABA = gamma-aminobutyric acid, PEMA = phenylethylmalonamide

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Using *Gingko biloba* Extract to Improve Cognitive Function

EGb 761, a *Gingko biloba* extract, has been associated with improved cognitive function in humans. In this study, 8 geriatric dogs with mild cognitive impairment were treated with the extract. Activity was measured using collar accelerometers; arterial (ie, femoral, carotid, middle cerebral) blood flow was measured using Doppler ultrasonography. Although no significant effect was detected on peripheral blood flow, a prolonged (≥ 6-day duration) dose-related increase in middle cerebral arterial blood flow was identified.

Source: The *Ginkgo biloba* special extract EGb 761® improves cerebral blood flow and behavioral activity in aged beagle dogs with mild cognitive dysfunction. Dobson H, Milgram B, Schramm E, Koch E. *AAVPT Biennial Symposium Proceedings* May 2013.

New Alternative for Feline Diabetes?

Effects of the thiazolidinedione insulin sensitizer pioglitazone were evaluated in obese, insulin-resistant cats to determine the sensitizer's potential as a therapeutic alternative for feline diabetes. Pioglitazone was administered PO in a placebo-controlled, 3-way crossover design. Significantly improved insulin sensitivity, reduced insulin AUC (area under the curve) during IV glucose tolerance testing, and lowered serum triglyceride and cholesterol concentrations were identified in the treated group. No adverse effects were noted.

Source: Effects of pioglitazone on insulin sensitivity and serum lipids in obese, insulin-resistant cats. Clark MH, Thomaseth K, Dirikolu L, et al. *AAVPT Biennial Symposium Proceedings* May 2013.

Drug Monitoring for Target Teriflunomide Levels

The immunomodulatory drug leflunomide is used to treat immune-mediated diseases in dogs. Its activity depends on the metabolic conversion of leflunomide to teriflunomide. Healthy dogs received leflunomide at 4 mg/kg, and leflunomide and teriflunomide levels were measured. Results suggested that predicting teriflunomide levels based on the leflunomide dose would be unsuccessful, supporting the need for drug monitoring.

Source: Pharmacokinetics of leflunomide and its metabolite teriflunomide. Sofge J, Bunn H, Cruz-Espindola C, et al. *AAVPT Biennial Symposium Proceedings* May 2013.