

Seizures - those darn things just keep coming back!

Long-term anticonvulsant management

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Overview

- ▶ Terminology
- ▶ Indications for AED therapy
- ▶ Drug options
 - ▶ Phenobarbital
 - ▶ Potassium bromide
 - ▶ Zonisamide
 - ▶ Levetiracetam
- ▶ Maximizing success

Terminology

- ▶ Seizure: clinical manifestation of a discrete episode of abnormal neuronal activity
 - ▶ Generalized - both hemispheres involved, always lose consciousness
 - ▶ Focal - only one hemisphere initially affected, variable effect on LOC and responsiveness
- ▶ Epilepsy: recurrent seizures of intra-cranial origin
 - ▶ Idiopathic - no structural abnormality, other neuro signs, age-dependent onset, known or suspected genetic cause
 - ▶ Secondary - identifiable brain lesion
 - ▶ Tumor, infectious/inflammatory disease, vascular accident, trauma, hydrocephaly, etc.
 - ▶ Cryptogenic - no apparent lesion, but dose not fit idiopathic criteria

Terminology

- ▶ Cluster seizures: two or more seizures within 24 hours
- ▶ Status epilepticus:
 - ▶ Single ictus lasting longer than 5 minutes
 - ▶ Two or more separate seizures without complete return to normal in between
- ▶ Reactive seizures: seizure brought about by a systemic perturbation
 - ▶ The brain itself is normal

When do you start AED therapy

- ▶ 3 yr old Labrador with presumed idiopathic epilepsy has a single seizure...
 - ▶ Once a year
 - ▶ Once every 6 months
 - ▶ Once every 3 months
 - ▶ Once a month
 - ▶ Once a week

Indications for AED therapy

- ▶ Any seizure frequency in the presence of structural disease
 - ▶ This includes animals with a history of brain disease or severe trauma
- ▶ Any patient that presents with cluster seizures or status epilepticus
- ▶ Unacceptable, prolonged, or severe postictal period
- ▶ More than one seizure every 3 months (or >2 seizures every 6 months)

Why that interval?

- ▶ AED therapy started earlier = better long-term control
- ▶ Start with single or few epileptic foci (pacemaker cells)
 - ▶ Recurrent seizures increase number of pacemaker cells = kindling
 - ▶ More pacemaker cells = more seizures
 - ▶ Mirror foci development
- ▶ Owner perception
 - ▶ Quality of life related to seizure frequency and drug side-effects

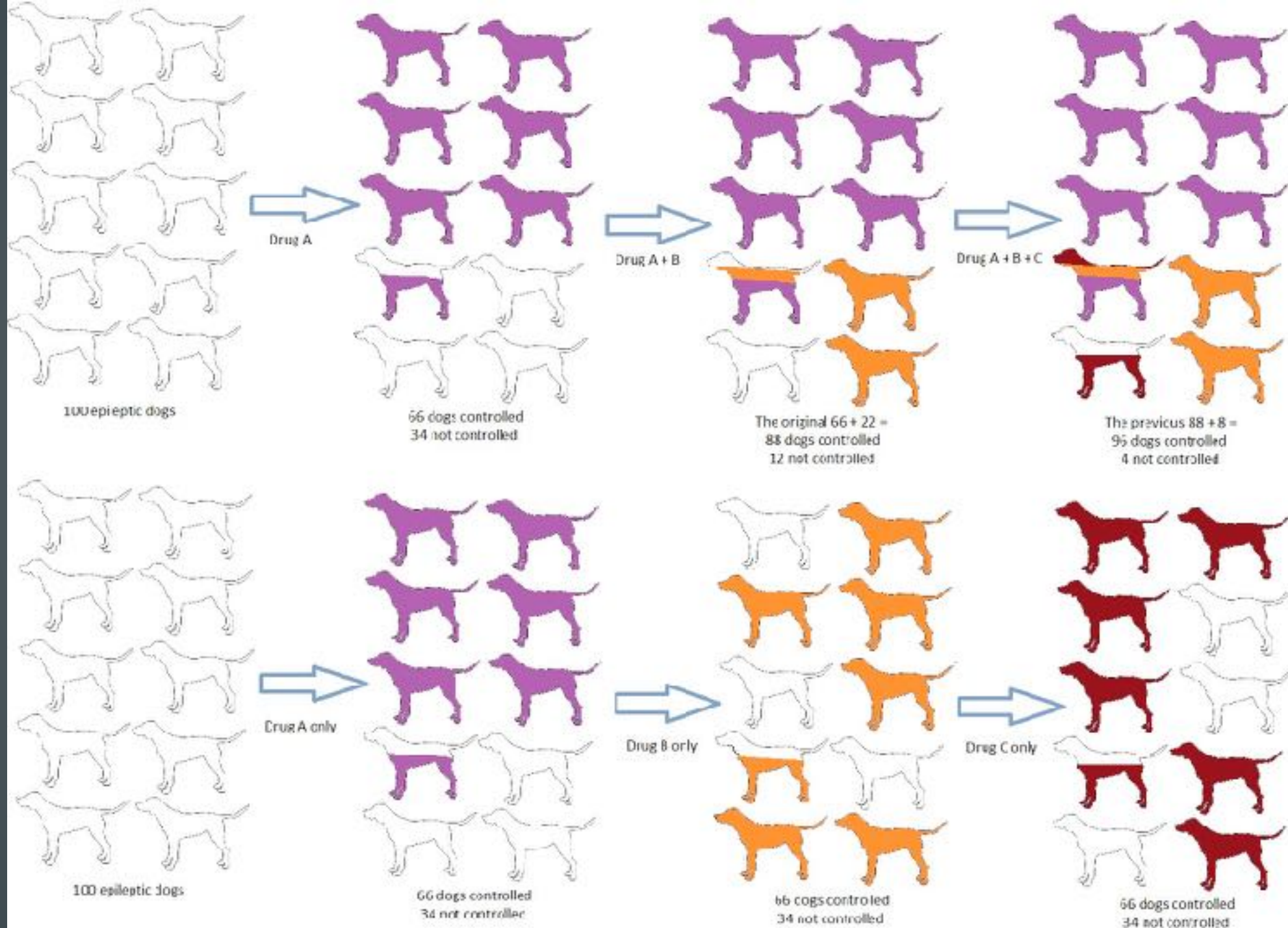
Owner counseling - a MUST

- ▶ Goal is to reduce seizure frequency & severity, rarely eliminated
- ▶ Medication is required for life - never change dose w/o veterinarian input
- ▶ Drug efficacy (and side effects) should not be judged for at least 4 weeks
- ▶ No single drug, dose, or drug combination that works in all cases
 - ▶ Adjustments to drugs and doses used should be expected
 - ▶ Right combination found by trial and error
- ▶ For cats:
 - ▶ Seizure severity does not correlate with how difficult they are to control

Where to start

- ▶ There is no clear consensus on what agent is the “best” at controlling seizures
 - ▶ Phenobarbital and KBr have been used the longest
 - ▶ Newer drugs have fewer side effects & may require less monitoring
 - ▶ Since these drugs are now generic costs are similar to older drug options
- ▶ FEW comparison studies (only imepitoin vs phenobarb)
- ▶ First-line (sole) agents include: phenobarbital, KBr, zonisamide, levetiracetam
 - ▶ Imepitoin may be available in 2020
- ▶ Secondary (add-on) agents include: above + gabapentin or pregabalin

A first-line drug will control ~2/3 of epileptic patients



Phenobarbital

- ▶ Induces its own metabolism and that of zonisamide & levetiracetam
- ▶ Starting dose 2.5-3 mg/kg q12 (PO or IV)
 - ▶ Can go up to 5 mg/kg, but only with guidance of drug levels
 - ▶ Takes ~10 days to reach steady state
 - ▶ Maximal levels 4-8 hours after oral dosing
- ▶ Loading: 16-20 mg/kg given over 24 hours
 - ▶ 4 x 4 mg/kg doses every 6 hours
 - ▶ Needs to be done in hospital
- ▶ Side effects
 - ▶ Common: Ataxia, sedation - worst for first few weeks, warn owner
 - ▶ Common: PU/PD, PP, weight gain, panting
 - ▶ Rare: Blood dyscrasias, liver toxicity

Phenobarbital

- ▶ **Monitoring:**
 - ▶ CBC/Chem/levels: 2 weeks, 6 weeks, every 6 months
 - ▶ Levels 2 weeks after any dosage change AND/OR with any sudden change in seizure frequency
- ▶ **Chemistry changes:**
 - ▶ Will induce ALP - can be significantly elevated
 - ▶ ALT may increase but usually not more than 5-6 x normal
 - ▶ Increases in bile acids, tбили, AST, or hypoalbuminemia indicate possible liver failure
 - ▶ Rapidly investigate and likely withdrawal drug
- ▶ **Therapeutic level: 15-35 mcg/ml**
 - ▶ >35 mg/ml → higher risk of bone marrow or liver toxicity

Primidone

- ▶ Converted to phenobarbital and other active metabolites
- ▶ Less efficacious than phenobarbital
- ▶ Higher rate of adverse events

- ▶ NOT recommended

Potassium bromide (KBr)

- ▶ Exclusively renally excreted - dose reduce (or use other) with kidney disease
- ▶ Chemistry & blood gas cannot distinguish Br from Cl → falsely increases Cl
- ▶ High salt diet or IVF with high Cl will increase elimination of bromide
- ▶ Side effects:
 - ▶ Ataxia, sedation - worst for first few weeks, worse w/ phenobarb, warn owner
 - ▶ Common: PU/PD, PP, weight gain
 - ▶ Rare: Pancreatitis, megaesophagus
 - ▶ Bromism
 - ▶ Profound sedation, weakness, ataxia, tremors, stupor
 - ▶ Typically if levels >300 mg/dL but can occur at lower levels
 - ▶ Treat by diuresing with 0.9% NaCl, start other AED

Potassium bromide

- ▶ Dose 30-80 mg/kg q24 alone OR 25-40 mg/kg q24 with phenobarbital
 - ▶ Gastric irritation and vomiting in some patients
 - ▶ Use liquid or divide dose
- ▶ Loading 400-600 mg/kg over 1-2 days
 - ▶ 4 x 100-150 mg/kg doses q12
- ▶ Monitoring
 - ▶ Levels at 1 month, 3 months, every 6-12 months
 - ▶ 1 month after any dose change AND/OR if any sudden change in seizure frequency
 - ▶ Annual renal panel to make sure no kidney disease
- ▶ Therapeutic level 100-300 mg/dl alone or 80-250 mg/dl with phenobarbital
- ▶ NOT recommended in cats - potentially fatal pneumonitis



Zonisamide

- ▶ Principally metabolized by liver, but some renal excretion
 - ▶ Phenobarb will increase its metabolism
- ▶ Reported to have a high safety margin
 - ▶ 30 mg/kg/day x 12 mo tolerated well, at 75 mg/kg/day saw liver changes
- ▶ Side effects:
 - ▶ Sedation, ataxia - typically improve over a couple weeks and less severe than PB/KBr
 - ▶ Vomiting rarely reported - typically resolves w/ acclimation
 - ▶ Technically a sulfa drug
 - ▶ Rare idiosyncratic liver failure and renal tubular acidosis reported (couple of each)
 - ▶ Liver failure reported within first two weeks

Zonisamide

- ▶ Dose 5-10 mg/kg q12 hours, can go up to 15 mg/kg with level guidance
 - ▶ If giving with phenobarbital start closer to 10 mg/kg
- ▶ Loading - double the maintenance dose x 3 days
 - ▶ Can load at home
 - ▶ Even during loading typically have mild sedation/ataxia
- ▶ Can give rectally at 3 x intended dose
- ▶ Monitoring:
 - ▶ Levels & chemistry: (+/- chem at 1 week), 2 weeks, every 6 months
 - ▶ Levels 2 weeks after dose change AND/OR sudden change in seizure frequency
 - ▶ Levels 2 weeks after addition of or change in phenobarb dosing
- ▶ Therapeutic level 10-40 mcg/ml

Example: 10 kg dog
Maintenance dose = 50 mg
Loading dose = 100 mg
Rectal loading dose = 300 mg

Levetiracetam (LV)

- ▶ 1/3 renally excreted the rest is hydrolyzed by various tissues
 - ▶ Phenobarbital does increase its metabolism
- ▶ SHORT half-life of 3-4 hours → REQUIRES q 8 hr dosing, NOT three times daily!
- ▶ Extremely safe drug doses of 1200 mg/kg/day only result in nausea/vomiting
- ▶ Minimal side effects even at high doses
 - ▶ Does not affect normal neuronal activity
 - ▶ May see sedation at higher doses

Levetiracetam

- ▶ Make sure owners can give q 8 hours!
- ▶ Starting dose is 20-40 mg/kg q 8 hours PO or IV
 - ▶ Increase in ~20 mg/kg increments
 - ▶ Peak plasma levels within 2 hours of oral dosing, immediate with IV dose
- ▶ Loading - some recommend 60 mg/kg loading dose to reach steady state
- ▶ Monitoring - levels not recommended
 - ▶ Therapeutic levels in animals not known (human 12-46 mcg/ml)
 - ▶ Testing is expensive and hard to find

Extended-release levetiracetam (ER or XR)

- ▶ Extended release formulations can be given every 12 hours
- ▶ Take total daily dose of regular levetiracetam and divide by 2 = XR dose
- ▶ ONLY available in 500 and 750 mg tablets
 - ▶ Cannot crush or cut tablets
- ▶ Slower time to onset and steady state
- ▶ May be more feasible for some owners.

Imepitoin

- ▶ Partial agonist at the benzodiazepine receptor - tolerance, dependence, and loss of efficacy do not occur
- ▶ Approved as AED in Europe since 2013, approved in US for noise phobia in 2018
- ▶ Owned by Boehringer Ingelheim
- ▶ May be marketed in US in 2020?
- ▶ Good long term studies (12 mo) demonstrate few side effects and good seizure control
 - ▶ Multi-center, randomized, blinded study it was as effective as PB with less adverse events
 - ▶ Toxicity studies show no adverse effects with high doses (150 mg/kg) for 26 weeks.

Gabapentin

- ▶ Secondary agent only
- ▶ Primarily renal excretion, but some liver metabolism
- ▶ Short half-life necessitates q 8 hour dosing when used as AED
- ▶ Dosing: 10-30 mg/kg q8 hours PO
 - ▶ Neurologists I have worked with recommend closer to 30 mg/kg for AED use
- ▶ Sedation and ataxia are major side effects
 - ▶ Can be profound, start with 10 mg/kg and work up
 - ▶ Worse in older animals and when added to other AEDs
- ▶ Routine monitoring not recommended

Pregabalin

- ▶ Similar to gabapentin but considered 3-10x more potent
 - ▶ May have more anticonvulsant activity compared to gabapentin
- ▶ Dosing: 4 mg/kg q8 hours
 - ▶ May start with 2 mg/kg and increase over time to limit side effects
- ▶ Side effects - sedation and ataxia
- ▶ Currently cost prohibitive for most owners

Benzodiazepines

- ▶ Dogs: short duration of action and tolerance rapidly develops
 - ▶ Rebound seizures w/ drug withdrawal
 - ▶ Ineffective for long term use
- ▶ Cats: longer drug half-life and tolerance is less common
 - ▶ MAY have role in epilepsy treatment
 - ▶ Fatal idiosyncratic liver necrosis reported with oral diazepam dosing
 - ▶ Chlorazepate has been used long term in cats
 - ▶ 3.75-7.5 mg/kg q 6-12 hours
 - ▶ Careful monitoring of liver function recommended

How to maximize success

- ▶ Medication schedule precision
- ▶ CHECK LEVELS
 - ▶ Verify owner compliance
 - ▶ Can help determine pharmacokinetic vs functional tolerance of a drug
- ▶ Maximize drug levels/dose before adding other drugs
- ▶ Do NOT remove an AED unless unacceptable side-effects occur
 - ▶ Add another drug in rather than stopping one and starting another
- ▶ Spay or neuter epileptic animals
 - ▶ Idiopathic epilepsy is often of genetic origin
 - ▶ Estrous cycle changes can precipitate seizures

Extra help for cluster seizures

- ▶ Important to have a plan for owner
 - ▶ If cannot quickly gain control at home requires hospitalization
 - ▶ 3 or more seizures in 24 hours or if status occurs = hospitalization
- ▶ If overall adequate control of event frequency focus on peri-event control
 - ▶ i.e. dog has one cluster event every 6 months, but during cluster has 6 seizures over a couple days
- ▶ If event frequency is inadequately controlled focus on every day (long term) AED plan first
 - ▶ i.e. dog has cluster event every 2 months

Peri-event strategies

- ▶ Give an extra dose of meds & continue regular schedule)
 - ▶ For phenobarbital, levetiracetam, zonisamide
 - ▶ Give an additional dose of regular AED(s) as soon as dog can be medicated
 - ▶ Up to 2x per event to try and break cycle of clusters
- ▶ Try levetiracetam pulse therapy
 - ▶ 20-60 (or more) mg/kg q8 for 3-5 days after first seizure of event
 - ▶ I recommend 50-60 mg/kg q8 range when using as pulse therapy
- ▶ For animals that have status - can have owners give intranasal midazolam or rectal valium at 2x standard dose
 - ▶ Midazolam autoinjectors being made for human use - maybe a possibility in future?

Cost comparison

| One Month Supply | PB 3 mg/kg BID | ZN 5 mg/kg BID | LV 25 mg/kg TID | LV 50 m/kg TID | LV - XR 50 mg/kg BID | Gabapentin 30mg/kg TID |
|------------------|----------------------|----------------------|-----------------------|----------------------|----------------------------|------------------------------|
| 10 kg dog | \$9-12 | \$9-17 | \$13-15 | \$9-18 | \$22-35 | \$11-20 |
| 30 kg dog | \$21-30 | \$23-35 | \$21-27 | \$40-55 | \$50-70 | \$28-40 |

- Have owners check with various pharmacies - VAST differences in prices can be seen
- Can try compounding pharmacies too
- Check various tablet sizes, especially with levetiracetam

Questions

