Diagnostic and Treatment Approach to Seizures and Epilepsy

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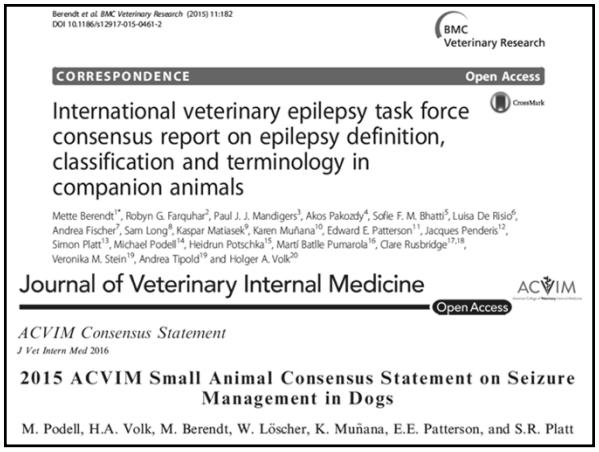
COLLEGE OF VETERINARY MEDICINE

Outline

- Definitions
- Seizure classification
- Epilepsy classification
- Causes of Seizures
- Diagnostic Approach
- Treatment
- Long-term monitoring



Berendt et al. BMC Veterinary Research (2015) 11:182
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BMC Veterinary Research

CORRESPONDENCE Open Access

International veterinary epilepsy task force consensus report on epilepsy definition, classification and terminology in companion animals

Mette Berendt[1*], Robyn G. Farquhar[2], Paul J. J. Mandigers[3], Akos Pakozdy[4], Sofie F. M. Bhatti[5], Luisa De Risio[6], Andrea Fischer[7], Sam Long[8], Kaspar Matiasek[9], Karen Muñana[10], Edward E. Patterson[11], Jacques Penderis[12], Simon Platt[13], Michael Podell[14], Heidrun Potschka[15], Martí Batlle Pumarola[16], Clare Rusbridge[17,18], Veronika M. Stein[19], Andrea Tipold[19] and Holger A. Volk[20]

Journal of Veterinary Internal Medicine Open Access

ACVIM Consensus Statement
J Vet Intern Med 2016

2015 ACVIM Small Animal Consensus Statement on Seizure Management in Dogs

M. Podell, H.A. Volk, M. Berendt, W. Löscher, K. Muñana, E.E. Patterson, and S.R. Platt

What is a seizure?

Paroxysmal period of abnormal cerebral function associated with great variety in clinical manifestations = *CLINICAL SIGN*

Reactive seizure – toxins

Epileptic seizure - epilepsy

What is Epilepsy?

Condition characterized by recurrent epileptic seizures of neural (intracranial) origin = *DISEASE*

2 or more seizures with interval of 24 hrs

Idiopathic epilepsy – 1% dogs

Seizure Classification

- Generalized epileptic seizures
- Focal epileptic seizures
- Focal epileptic seizures with secondary generalization

IVETF, BMC Vet Res, 2015

Generalized Epileptic Seizure (Convulsion, *Grand mal?*)

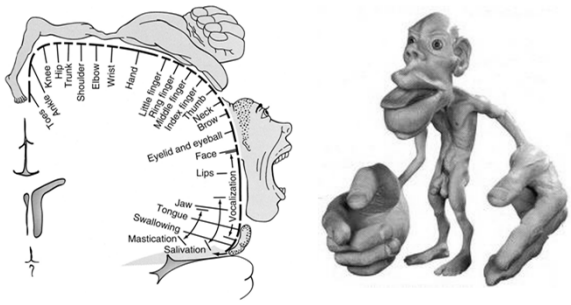
- Unconscious (except myoclonic seizures)
- Autonomic signs
- Tonic-clonic
- Tonic
- Clonic
- Myoclonic
- Atonic
- Duration – usually < 2 minutes
  - *Idiopathic epilepsy, metabolic or toxic disturbances*

Focal Epileptic Seizures

- No longer differentiate simple and complex focal seizures (consciousness intact or not)
- Focal motor activity contralateral affected cortex
- Facial involvement
- Can be autonomic, behavioral
- Duration: variable
  - *Structural cortical abnormalities*
  - *Idiopathic epilepsy some breeds (Lagotto R.)*

Human Motor Cortex

Penfield and Rasmussen's Homunculus



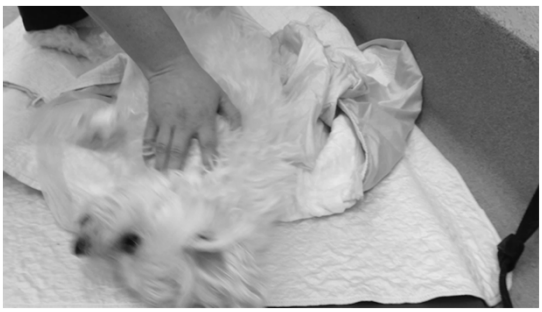
Guyton, Textbook Medical Physiology, p. 635

Focal seizure with secondary generalization

- Focus on motor area - visible
- Focus non-motor area – difficult to identify
- Watch carefully beginning
  - *Structural cortical abnormalities*
  - *Idiopathic epilepsy some breeds*

Walle
Pekingese
3 YR
MC
#403537

Zoey, Maltese, 7 years, FS



"Pingo"
Mixed breed dog
Male
4-months-old

"Sasha"
Rottweiler
2-year-old
Female
OVC 234594

Other Episodic events

- Vestibular crisis
- Cervical pain
- Syncopal events
- Narcolepsy/cataplexy
- Tremors
- Behavioural disorders
- Paroxysmal diskinesias
- Acute weakness (Myasthenia)
- Sleep disorders

What are the causes of seizures?

Extracranial
and
Intracranial

Extracranial

- Toxins
  - Strychnine
  - Organophosphates
  - Carbamates
  - Lead
  - Mycotoxins
- Metabolic
  - Hypoglycemia
  - Hypocalcemia
  - Polycythemia (cats)
  - Uremic encephalopathy
  - Hepatic encephalopathy
    Not very common

Incidence and risk factors for neurological signs after attenuation of single congenital portosystemic shunts in 253 dogs

Veterinary Surgery. 2018;**47:**745–755.

Rhiannon Strickland BVetMed[1] | Michael S. Tivers BVSc, PhD, DipECVS[2] | Sophie E. Adamantos BVSc, DACVECC, DECVECC[3] | Tom R. Harcourt-Brown MA, VetMB, DipECVN[3] | Robert C. Fowkes BSc, PhD[4] | Victoria J. Lipscomb MA, VetMB, DipECVS[1]

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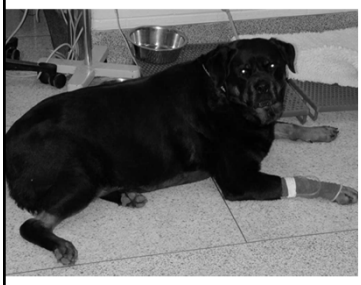
Median duration of clinical signs prior to surgery was 57 days (range 5-1436). The severity of HE prior to medical management was graded as 1 in 71 (28.1%) dogs, 2 in 108 (42.7%) dogs, 3 in 72 (28.5%) dogs, and 4 in 2 (0.8%) dogs.

TABLE 1 Grading system used to evaluate the severity of HE prior to medical therapy in dogs[a]

HE Grade	Clinical signs
1	Normal, absence of abnormal clinical signs
2	Lethargy, apathy, minimal disorientation, subtle personality change, inappropriate behavior
3	Hypersalivation, severe ataxia, somnolence but responds to verbal stimuli, circling, head pressing
4	Coma, stupor, repeated seizures

(grade 3) in 13 (46.4%) dogs. Twelve (42.9%) dogs suffered postoperative generalized seizures (Table 6). Among the 28

Insulinomas



Classification of Epilepsy

- Idiopathic (Genetic, Primary)
  - Functional cerebral dysfunction
  - Hereditary
- Structural (Symptomatic, Secondary)
  - Intracranial disease – progressive or not
- Unknown (Presumed symptomatic, cryptogenic)
  - Structural epilepsy is suspected but cannot be confirmed with the available diagnostic methods

Berendt et al. BMC Vet Res, 2015

Idiopathic Epilepsy

- Very common disease dogs
- Hereditary basis proven in:
  - Long- medium nosed breeds - German shepherds, Beagles, Golden retriever, Bernese mountains, Springer Spaniels
  - Rare in brachicephalic breeds
- Onset seizures usually 6 m- 6 years of age
- Generalized epileptic or focal with sec. general.
- Normal PE, Neuro exam, MRI, CSF

Diagnostic Approach

2 Main Questions:

1 – *Is the event really a seizure?*

Define it based on detailed history and, if possible, video recording of episodes

2 – *If yes, what is causing it?*

Approach - Cause

First: *Rule-out extracranial causes*

Signalment, history, physical examination, CBC, biochemistry profile, UA

+/- bile acids, insulin, lead level

Second: *Look for evidence of brain disease*

Neurological examination

MRI, CT, CSF, EEG?

Idiopathic Epilepsy – 6m-6yrs, 2 or more seizures interval 24h, PE, NE, blood work all normal

Neurological Examination

- Interictal period (if possible serial examinations)
- Dogs post status epilepticus can have neurological deficits for up to 2 weeks
- Key tests (assess thalamocortical function):
  - Mental status - behavior
  - Menace response
  - Nasal sensation
  - Postural reactions (proprioception)

  Watch mainly for asymmetrical responses
- Normal NE – likely idiopathic epilepsy
- Abnormal – structural or functional disease

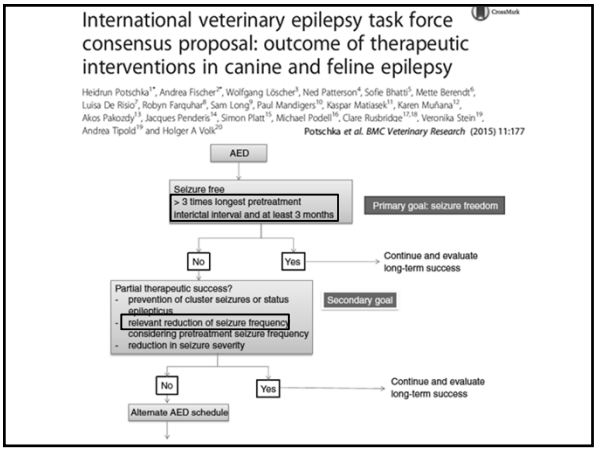
Treatment

Fundamentals

- Goals of antiepileptic therapy
- When to start?
  - *After 2nd seizure, interval < 6- months, dogs with idiopathic epilepsy < 2 years, cluster seizures*
- When to wait? Interval > 6 months
- When to discontinue treatment?
  - *Can attempt if more than 1 year seizure-free*
  - *Discontinue slowly – reduce 25% every 2-4 wks*

Which antiepileptic drugs can we use safely for long-term treatment in dogs?

- Phenobarbital
- Potassium (or sodium) Bromide
- Zonisamide
- Levetiracetam
- Gabapentin
- Pregabalin
- Topiramate
- Chlorazepate



Phenobarbital

- Effective 83% cases, safe, low cost
- Mechanism action
  - Increase responsiveness GABA
  - Antiglutamate effects
- Hepatic metabolism
- Dose
  - Dogs and cats – initially 2.5 mg/kg q12h
  - Puppies – start with 5 mg/kg q12h
- Therapeutic (safe and effective) serum level
  - 20-35 μg/ml (ideal level 23-30 μg/ml)
- Steady-state concentrations in 2 weeks

Question!!

- Ronaldo!!! I am treating a canine creature with phenobarbiltal. I already doubled the dose (started with 2.5 mg/kg and now I am at 5…).
- It is not working, tell me which other medication I should use now??

TABLE 1—Dosages, hours, and serum concentrations for dogs given phenobarbitol, grouped according to efficacy

Effective			Not effective		
Dosage*	Hours	Concentration†	Dosage*	Hours	Concentration†
16.8	8	81.3	19.9	7	42.7
16.0	9	14.4	14.4	7	43.2
12.5	9	34.1	14.0	9	25.3
12.0	12	46.1	13.3	12	33.5
11.2	4	30.2	10.2	10	28.4
10.5	8	39.7	10.0	12	18.4
10.2	12	45.1	7.4	12	17.3
8.8	12	32.1	5.8	5	16.2
6.4	9	19.7	5.5	10	11.2
5.7	3	18.9	5.5	10	14.0
5.0	8	18.1	5.4	9	17.1
4.4	6	14.2	5.3	10	26.8
4.4	6	21.5	5.2	12	19.0
4.4	8	23.2	4.9	8	17.2
4.2	12	14.6	4.8	5	15.2
4.2	16	22.3	4.3	6	20.4
4.1	3	15.4	4.1	6	14.3
3.4	12	22.0	4.0	10	17.8
1.6	15	21.4	3.2	12	17.9
1.2	13	6.5	2.3	12	12.5
...	...	...	1.2	15	4.7
			0.3	2	13.1

Farnbach JAVMA, 184:1984

Phenobarbital – Side-effects

- Sedation, PU/PD
- Tolerance – functional or metabolic
- Hepatotoxicity
  - High levels, long periods
- Bone marrow suppression (4.2%)
- Superficial necrolytic dermatitis

Potassium Bromide (KBr) – Characteristics/Advantages

- Used as sole drug or with phenobarbital
- Effective 65-83% dogs, safe, low cost
- Does not undergo hepatic metabolism, intact renal excretion
- Mechanism action
  - Hyperpolarize neuronal membranes – Bromide diffuses through chloride channels 1.5 times more than chloride (-110/-120 mv)
- Once a day dosing

Potassium Bromide (KBr)

- Dose dogs: 30-60 (40 or >) mg/Kg q24h
  - Long half-life – 15-25 days
  - Steady-state - +/- 3-4 months (5 half-lives)
- Ideal serum concentrations - 150-300 mg/dL
  March et al., J Vet Pharm Therap 2002 – 60 mg/kg/day concentration 245 mg/dL
- Loading modified (600 mg/kg)
  40 mg/kg q12h for 15 days, then 40 mg/kg q24h
- *KBr is contraindicated in cats*

Comparison of phenobarbital with bromide as a first-choice antiepileptic drug for treatment of epilepsy in dogs

Dawn Merton Boothe, DVM, PhD, DACVIM, DACVCP; Curtis Dewey, DVM, MS, DACVS, DACVIM; David Mark Carpenter, PhD

JAVMA, Vol 240, No. 9, May 1, 2012

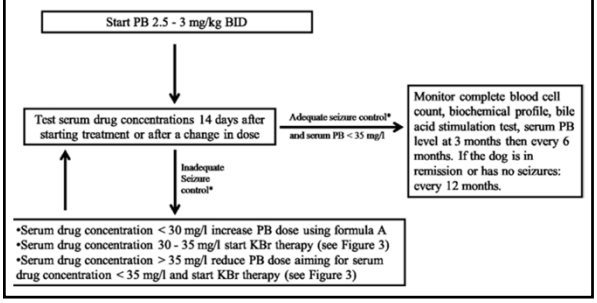
Results—Phenobarbital treatment resulted in eradication of seizures (17/20 [85%]) significantly more often than did bromide (12/23 [52%]); phenobarbital treatment also resulted in a greater percentage decrease in seizure duration (88 ± 34%), compared with bromide (49 ± 75%). Seizure activity worsened in 3 bromide-treated dogs only. In dogs with seizure

REFRACTORY EPILEPSY

practice: "*Drug resistant epilepsy is defined as failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom*" [1]. This definition has been the source of much

International Veterinary Epilepsy Task Force consensus proposal: medical treatment of canine epilepsy in Europe *BMC Veterinary Research* (2015) 11:176

Sofie F.M. Bhatti[1*], Luisa De Risio[2], Karen Muñana[3], Jacques Penderis[4], Veronika M. Stein[5], Andrea Tipold[5], Mette Berendt[6], Robyn G. Farquhar[7], Andrea Fischer[8], Sam Long[9], Wolfgang Löscher[10], Paul J.J. Mandigers[11], Kaspar Matiasek[12], Akos Pakozdy[13], Edward E. Patterson[14], Simon Platt[15], Michael Podell[16], Heidrun Potschka[17], Clare Rusbridge[18,19] and Holger A. Volk[20]



Newer Antiepileptics

- Zonisamide (sulfa derivate)
  - Good option for "mild" epileptics
  - 10 mg/kg q12h
  - Efficacy – 60% (Dewey 2004, Von Klopmann, 2007)
- Levetiracetam
  - 20 mg/kg q8h
  - Extended release (ER) can be used q12h
  - No hepatic metabolism– ideal for patients w liver disease
  - 60-65% efficacy (Volk et al 2008; Packer et al 2015, Fredso et al 2016)

Safety profile of these newer drugs is much better

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ACVIM Consensus Statement

J Vet Intern Med 2016

2015 ACVIM Small Animal Consensus Statement on Seizure Management in Dogs

M. Podell, H.A. Volk, M. Berendt, W. Löscher, K. Muñana, E.E. Patterson, and S.R. Platt

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

	Monotherapy recommendation			Risks Types				Add-on AED recommendation	
Drug	Level	Grade	Monitor drug levels	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

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

The Veterinary Journal
journal homepage: www.elsevier.com/locate/tvjl

A single-blinded phenobarbital-controlled trial of levetiracetam as mono-therapy in dogs with newly diagnosed epilepsy

N. Fredsø [a,*], A. Sabers [b], N. Toft [c], A. Møller [d], M. Berendt [a]

Veterinary Journal 208 (2016) 44–49

Table 2
Comparison of the outcome measures in the two treatment groups, levetiracetam and phenobarbital.

	Dog		Breed	Sex	Months of inclusion	Monthly number of seizures baseline	Monthly number of seizures at exclusion	St (
LEV group	1	Bichon Havanese	ME	2	1.2	2.54		
	2	English Springer Spaniel	MN	5	1.55	1.89		
	7	Border Collie	ME	4	2.79	1.81		
	8	Small mixed breed	FE	13	1.14	0		
	9	Cocker Spaniel	FE	12	2.5	0.89		
Median				12	2.65	0.415		

In the levetiracetam treated dogs there was no significant difference in the monthly number of seizures before and after treatment, whereas in the phenobarbital treated dogs there were significantly ($P = 0.013$) fewer seizures after treatment. Five phenobarbital treated dogs were classified as true responders (≥50% reduction in seizures/month) whereas none of the levetiracetam treated dogs fulfilled this criterion. Adverse effects were reported in both groups but were more frequent in the phenobarbital group. In this study levetiracetam was well tolerated but was not effective at the given doses as monotherapy in dogs with idiopathic epilepsy.

Randomized blinded controlled clinical trial to assess the effect of oral cannabidiol administration in addition to conventional antiepileptic treatment on seizure frequency in dogs with intractable idiopathic epilepsy

Stephanie McGrath DVM
Lisa R. Bartner DVM, MS
Sangeeta Rao BVSc., PhD
Rebecca A. Packer DVM
Daniel L. Gustafson PhD

JAVMA | JUN 1, 2019 | VOL 254 | NO. 11

OBJECTIVE
To assess the effect of oral cannabidiol (CBD) administration in addition to conventional antiepileptic treatment on seizure frequency in dogs with idiopathic epilepsy.

DESIGN
Randomized blinded controlled clinical trial.

ANIMALS
26 client-owned dogs with intractable idiopathic epilepsy.

PROCEDURES
Dogs were randomly assigned to a CBD (n = 12) or placebo (14) group. The CBD group received CBD-infused oil (2.5 mg/kg [1.1 mg/lb], PO) twice daily for 12 weeks in addition to existing antiepileptic treatments, and the placebo group received noninfused oil under the same conditions. Seizure activity, adverse effects, and plasma CBD concentrations were compared between groups.

RESULTS
2 dogs in the CBD group developed ataxia and were withdrawn from the study. After other exclusions, 9 dogs in the CBD group and 7 in the placebo group were included in the analysis. Dogs in the CBD group had a significant (median change, 33%) reduction in seizure frequency, compared with the placebo group. However, the proportion of dogs considered responders to treatment (≥ 50% decrease in seizure activity) was similar between groups. Plasma CBD concentrations were correlated with reduction in seizure frequency. Dogs in the CBD group had a significant increase in serum alkaline phosphatase activity. No adverse behavioral effects were reported by owners.

CONCLUSIONS AND CLINICAL RELEVANCE
Although a significant reduction in seizure frequency was achieved for dogs in the CBD group, the proportion of responders was similar between groups. Given the correlation between plasma CBD concentration and seizure frequency, additional research is warranted to determine whether a higher dosage of CBD would be effective in reducing seizure activity by ≥ 50%. (*J Am Vet Med Assoc* 2019;254:1301–1308)

Treatment effects
Following study treatment, a significant ($P = 0.01$) reduction was identified in the group median for mean monthly seizure frequency in the CBD group (33%; median value before and after study treatment, 4.0 and 2.7, respectively), compared with that in the placebo group (0%; 2.0 and 2.0, respectively). Two dogs in the CBD group were classified as responders, compared with 2 dogs in the placebo group ($P > 0.99$; **Supplementary Table S1**, available at avmajournals.

Discussion

In the present study, a significant reduction in seizure frequency was achieved in dogs with intractable idiopathic epilepsy receiving CBD-infused oil as administered, compared with findings for dogs in the placebo group. Although the sample size was small, it quency and plasma CBD concentration. However, no significant difference was identified between treatment groups when the proportion of responders (≥ 50% decrease in seizure activity), which was perhaps a more clinically relevant outcome variable, was compared between groups.

J Vet Intern Med 2010;24:166–170

Placebo Effect in Canine Epilepsy Trials

K.R. Muñana, D. Zhang, and E.E. Patterson

Table 1. Seizure frequency relative to baseline during administration of active treatment epilepsy trials.

	Number (%) of Dogs with Decrease in Seizures		Number (%) of Dogs Classified as Responders[a]	
	Active	Placebo	Active	Placebo
Surgical implant	6/9 (67)	6/9 (67)	3/9 (33)	0/9 (0)
Novel drug	12/14 (86)	11/14 (79)	8/14 (57)	5/14 (36)
Dietary modification	3/6 (50)	5/5 (100)	1/6 (17)	3/5 (60)

[a]Responders: dogs with a ≥ 50% reduction in seizure

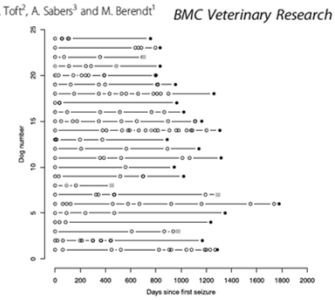
Regression to the mean is a statistical term used to describe the fluctuations of biological variables that occur over time and take the form of a sine wave around the mean.[11] Epilepsy is a waxing and waning disorder, and fluctuations in seizure frequency are common over the course of the disease. Owners are most likely to seek a change in therapy for their pet when seizures are under poor control. Over the short term, improvement in the seizure frequency is probable, regardless of the treatment administered. However, this improvement is often erroneously attributed to a recently instituted change in therapy, whereas in fact it is because of an effect of time.

RESEARCH ARTICLE

A prospective observational longitudinal study of new-onset seizures and newly diagnosed epilepsy in dogs

N. Fredsø[1*], N. Toft[2], A. Sabers[3] and M. Berendt[1]

BMC Veterinary Research (2017) 13:54



Long-term Monitoring

- Serum concentrations 6/6 months or after several seizures
- Phenobarbital always increase serum ALT, ALP
  - Does not indicate liver failure
  - ALT much higher than ALP - Toxicity?
- To assess liver function – Bile acids
- Recheck and monitor (mainly on dogs on PB):
  - Oral dose and serum concentration
  - Albumin, BUN, cholesterol, glucose, bilirubin, ALT, AST
  - Seizure log

Treatment Failures

- *Low oral dose*
- *Failure to make necessary adjustments in serum concentration*
- Inadequate client education
  - Inconsistent diet - KBr
- Poor owner compliance
- Tolerance
- Progressive disease
- Large breed dogs

Summary

- Confirm that the event is really a seizure
- Client education
- Perform a neurological examination
  - Remember the thalamocortical tests
- Most dogs with chronic seizures and normal neurological examination have idiopathic epilepsy
- Phenobarbital is still the most effective medication – when properly used
- When need to add a second AED, keep the first until reach steady state of the second - compare