Canine Seizure Management: Update on the ACVIM and IVETF Consensus Statements

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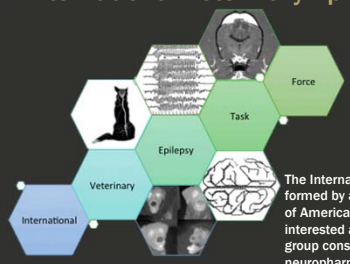
International Veterinary Epilepsy Task Force



The International Veterinary Epilepsy TaskForce (IVETF) is formed by a mondial (among others Europe, United States of America, Australia) group of (veterinary) scientists interested and specialised in the field of epilepsy. Our group consists of clinical veterinary neurologists, neuropharmacologists, and veterinary neuropathologists
http://www.ivetf.org/

Berendt et al. BMC Veterinary Research (2015) 11:182
International veterinary epilepsy task force consensus report on epilepsy definition, classification and terminology in companion animals

Hülsmeyer et al. BMC Veterinary Research (2015) 11:175
International Veterinary Epilepsy Task Force's current understanding of idiopathic epilepsy of genetic or suspected genetic origin in purebred dogs

Rusbridge et al. BMC Veterinary Research (2015) 11:194
International Veterinary Epilepsy Task Force recommendations for a veterinary epilepsy-specific MRI protocol

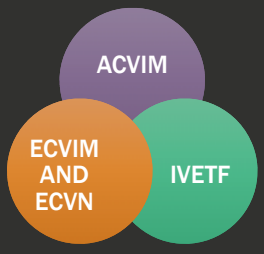
De Risio et al. BMC Veterinary Research (2015) 11:148
International veterinary epilepsy task force consensus proposal: diagnostic approach to epilepsy in dogs

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

Potschka et al. BMC Veterinary Research (2015) 11:177
International veterinary epilepsy task force consensus proposal: outcome of therapeutic interventions in canine and feline epilepsy

International Approach

- Standardization of terminology
- Provide foundation of scientific evaluation and recommendation
- Establish a framework for veterinary clinical and human translation studies
- Parallel work with International Veterinary Epilepsy Task Force



CON-SEN-SUS

- Latin from consentire (to allow)
- General agreement: unanimity
  - The judgment arrived at by most of those concerned
- **Group** solidarity in sentiment and belief

Our Approach

Problems

- Epilepsy is a heterogeneous disease process
- Incomplete diagnostic capabilities
- Unpredictable clinical outcome
- Wide-variability in treatment approaches
- Small database of strong evidence-based clinical studies
- Use of antiepileptic drugs (AED) established for people

Objectives

- Present a working clinical consensus statement for canine seizure management
  - Focus on epilepsy of undetermined cause (idiopathic/genetic/primary)
  - Chronic treatment only
- Recommendations based on published reports and clinical expertise opinion
- Establish a predetermined, concise and logical sequential approach to seizure management

Guidelines for the Diagnosis and Treatment of Canine Epilepsy

- Seizure identification and diagnosis (not included in this paper)
- Decision making treatment strategies
  1. When should treatment be started?
  2. Which drug should be used first?
  3. How should AED monitoring be performed?
  4. What are the risks of treatment?
  5. What is drug-resistance?
  6. When and which second AED should be started?
- Complimentary and alternative treatment strategies
- Guidelines to enhance patient response and quality of life
- Emergency treatment strategies (not included in this paper)

METHODOLOGY

Published evidence in the peer-reviewed literature

- 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
- Studies were included following modified criteria laid out in detail by Charalambous et al. 2014
  - Any peer-reviewed study without language restrictions in which an antiepileptic drug was used and in dogs with epilepsy
- Proceedings
  - Annual Congresses of the European Society and College of Veterinary Neurology and the American College of Veterinary Internal Medicine

Level Of Evidence	Type Of Evidence	Grade Of Recommendation
I	*Appropriately designed, controlled trials* Blinded, randomized clinical trials and drug efficacy of ≥50% seizure reduction for at least 6 months	A High and likely to be effective
IB	Blinded, randomized clinical trials and drug efficacy of ≥50% seizure reduction for at < 6 months	
II	*Case-control or cohort studies (N ≥ 15)* Non-blinded, randomized, or non-blinded and non-randomized clinical trials and/or drug efficacy of ≥50% seizure reduction for ≥ 12 weeks	B Moderate and likely to be effective
III	*Case-control or cohort studies: (N< 15)* Non-blinded and non-randomized clinical trials with cohort size of less than 15 and/or drug efficacy of ≥50% seizure reduction for < 12 weeks	C Low and may not be effective
IV	*Expert opinion only* without documentation by case reports or series	D Not recommended

Levels of evidence and grades of recommendation. Table adapted from the National Institute for Health and Care Excellence (NICE) guidelines (Eccles & Mason 2001)

Cochrane Risk of Bias Assessment Tool

Charalambous et al. Treatment in canine epilepsy- a systematic review. BMC Veterinary Research, 2014

- Random sequence generation
- Allocation concealment
- Blinding of participants
- Personnel and outcome assessors
- Completeness of outcome data
- Selective reporting of outcome measures
- Other sources of bias

When Should Treatment Be Started?

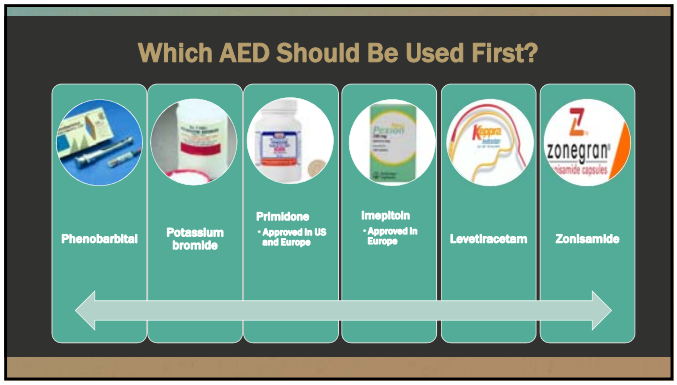
- Decision to treat is a reflection of the treatment goals:
  - Reduce or eliminate epileptic events
  - Reduce seizure severity
  - Avoid adverse effects
  - Reduce seizure-related mortality and morbidity
- Risk factors for seizure recurrence are not well-established for dogs
- Seizure density is considered a strong risk factor for seizure recurrence
  - Packer et al. Clinical risk factors associated with AED responsiveness in canine epilepsy, 2014 http://journals.plos.org/plosone/

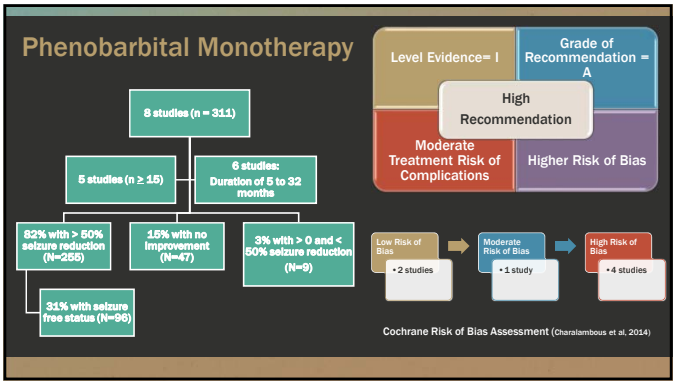
- Guidelines for people to start AED:
  - Diagnosis of current or previous defined cerebral lesions or trauma
  - Presence of inter-ictal EEG epileptic discharges (up to 90 % recurrence rate)
  - History of marked post-ictal adverse effects
  - First unprovoked, seizure for adult onset?
    - Individual risk and quality of life assessment
    - Recurrence risk 21-45% within first 2 years
    - Immediate treatment improves seizure free prediction by 50%

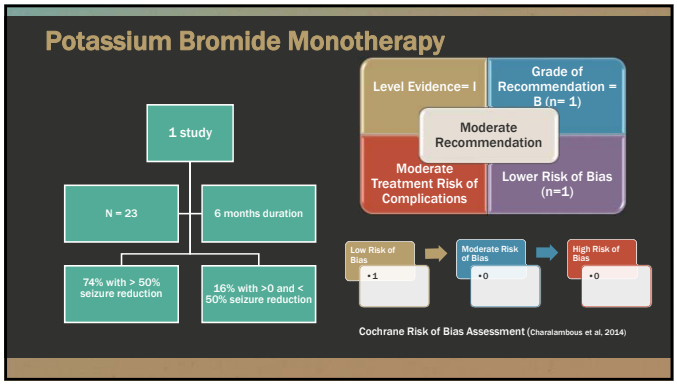
American Academy of Neurology, Summary of Evidence – Based Guidelines, 2015

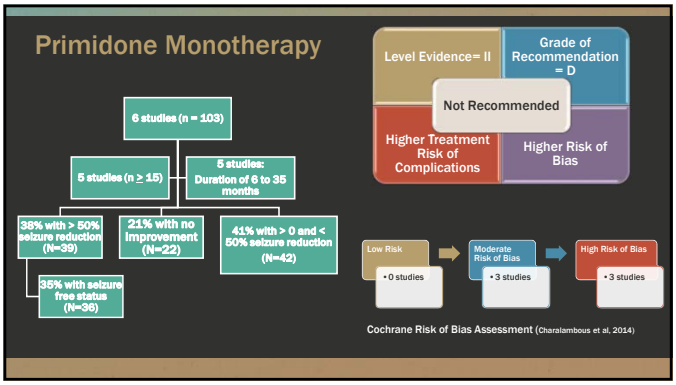
ACVIM Panel Recommendations: The Reasons to Start AED Therapy

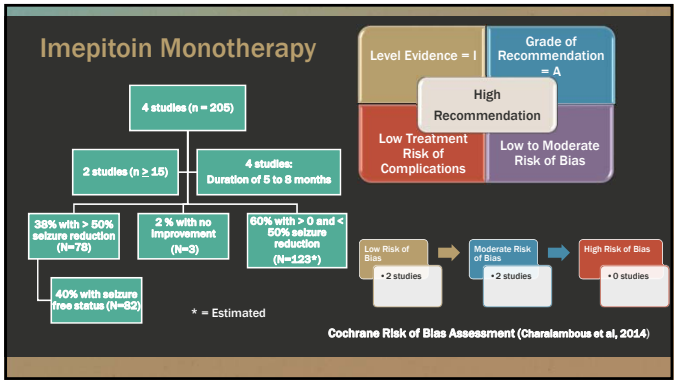
- Identifiable structural lesion present or prior history of brain disease or injury
- Acute repetitive seizures / status epilepticus has occurred
  - Ictal event ≥ 5 minutes or
  - 3 or more generalized seizures occur within a 24 hour period or
  - 2 or more seizures without completely regaining consciousness between seizures
- Two or more seizure events occur within a 6 month period
- Prolonged, severe, or unusual post-ictal periods occur
- IVETF : "The epileptic seizure frequency and/or duration is increasing and/or seizure severity is deteriorating over 3 inter-ictal periods"

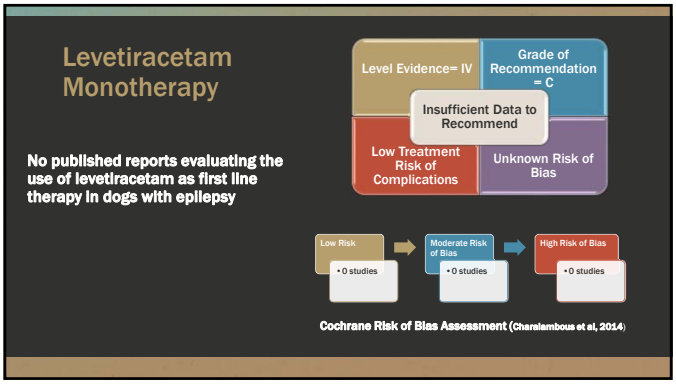

Which AED Should Be Used First?
Phenobarbital
Potassium bromide
Primidone
• Approved in US and Europe
Imepitoin
• Approved in Europe
Levetiracetam
Zonisamide
zonegran


Phenobarbital Monotherapy
8 studies (n = 311)
5 studies (n ≥ 15)
6 studies: Duration of 5 to 32 months
82% with > 50% seizure reduction (N=255)
15% with no improvement (N=47)
3% with > 0 and < 50% seizure reduction (N=9)
31% with seizure free status (N=96)
Level Evidence= I
Grade of Recommendation = A
High Recommendation
Moderate Treatment Risk of Complications
Higher Risk of Bias
Low Risk of Bias
• 2 studies
Moderate Risk of Bias
• 1 study
High Risk of Bias
• 4 studies
Cochrane Risk of Bias Assessment (Charalambous et al, 2014)

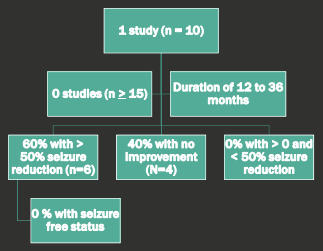

Potassium Bromide Monotherapy
1 study
N = 23
6 months duration
74% with > 50% seizure reduction
16% with >0 and < 50% seizure reduction
Level Evidence= I
Grade of Recommendation = B (n= 1)
Moderate Recommendation
Moderate Treatment Risk of Complications
Lower Risk of Bias (n=1)
Low Risk of Bias
• 1
Moderate Risk of Bias
• 0
High Risk of Bias
• 0
Cochrane Risk of Bias Assessment (Charalambous et al, 2014)

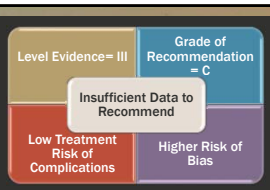

Primidone Monotherapy
6 studies (n = 103)
5 studies (n ≥ 15)
5 studies: Duration of 6 to 35 months
38% with > 50% seizure reduction (N=39)
21% with no improvement (N=22)
41% with > 0 and < 50% seizure reduction (N=42)
35% with seizure free status (N=36)
Level Evidence= II
Grade of Recommendation = D
Not Recommended
Higher Treatment Risk of Complications
Higher Risk of Bias
Low Risk
• 0 studies
Moderate Risk of Bias
• 3 studies
High Risk of Bias
• 3 studies
Cochrane Risk of Bias Assessment (Charalambous et al, 2014)


Imepitoin Monotherapy
4 studies (n = 205)
2 studies (n ≥ 15)
4 studies: Duration of 5 to 8 months
38% with > 50% seizure reduction (N=78)
2 % with no improvement (N=3)
60% with > 0 and < 50% seizure reduction (N=123*)
40% with seizure free status (N=82)
* = Estimated
Level Evidence = I
Grade of Recommendation = A
High Recommendation
Low Treatment Risk of Complications
Low to Moderate Risk of Bias
Low Risk of Bias
• 2 studies
Moderate Risk of Bias
• 2 studies
High Risk of Bias
• 0 studies
Cochrane Risk of Bias Assessment (Charalambous et al, 2014)


Levetiracetam Monotherapy
No published reports evaluating the use of levetiracetam as first line therapy in dogs with epilepsy
Level Evidence= IV
Grade of Recommendation = C
Insufficient Data to Recommend
Low Treatment Risk of Complications
Unknown Risk of Bias
Low Risk
• 0 studies
Moderate Risk of Bias
• 0 studies
High Risk of Bias
• 0 studies
Cochrane Risk of Bias Assessment (Charalambous et al, 2014)

Zonisamide Monotherapy





Cochrane Risk of Bias Assessment (Charalambous et al, 2014)

ACVIM Panel Monotherapy Recommendations:

DRUG	LEVEL OF EVIDENCE	GRADE OF RECOMMENDATION
Phenobarbital	I	A
Bromide	I	B
Primidone	II	D
Imepitoin	I	A
Levetiracetam	IV	C
Zonisamide	III	C

ACVIM Panel Grade of Recommendations (Level of Evidence) for AED Monotherapy

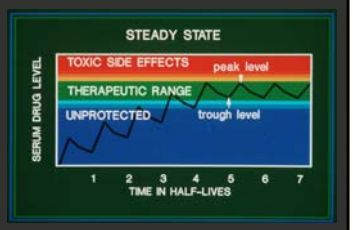
A (HIGH)	B (MODERATE)	C (LOW)	D (NO)
• Phenobarbital (I) • Imepitoin (I)	• Bromide (I)	• Levetiracetam (IV) • Zonisamide (III)	• Primidone (II)

How Should AED Monitoring Be Performed?

- Objectives
  - Determine effective drug levels after initiation of successful therapy (as appropriate)
  - Determine if drug failure is due to:
    - Pharmacokinetic factors to focus on a change in dose (metabolic tolerance) or
    - Pharmacodynamic factors to focus on a change of *drugs* (functional tolerance)
  - Determine if treatment failure is due to poor compliance, an inadequate or a change in drug level
  - Prevent toxic effects from occurring
  - Aid with individualization of therapy

Drug Monitoring

- *Reference range* is established by laboratory /clinical study for a *population*
  - Sub-therapeutic: Lower limit below which therapeutic response is unlikely
  - Toxicity: Upper limit below which toxic response is likely
- *Therapeutic range* is the range of drug concentrations associated with best achievable results in an *individual*
  - Initial
  - Target

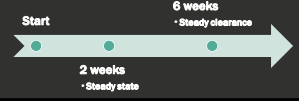


Phenobarbital

Evidence level: I

Grade of Recommendation for Monitoring: A

- Pharmacology
  - Elimination half-life of 24-40 hours
  - Auto-induction of hepatic metabolism results in enhanced clearance over 6 weeks
  - High degree of drug-drug interactions due to hepatic metabolism and higher protein binding
- Panel recommendations
  - Initial dose of 2.5 mg/kg q 12 hours
  - Monitor levels at 2 and 6 weeks and every 6 months,
    - 2 weeks after a dose change or with increase in seizure frequency
  - Monitor if signs of toxicity
  - Patient therapeutic range of 15-35 ug/ml
  - Collect trough sample for dogs with recurrent seizures

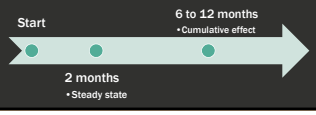


Potassium Bromide

Evidence level: I

Grade of Recommendation for Monitoring: A

- Pharmacology
  - Elimination half-life 15-20 days
  - Renal elimination
  - No protein binding
- Panel recommendations:
  - Initial dose of 30 to 40 mg/kg /day (single or divided)
  - Monitor at 8 to 12 weeks after initiation and every 12 months
    - 1 month after a dose change, or if increase in seizure frequency
  - Monitor if signs of toxicity
  - Patient therapeutic range is 1000 to 3000 ug/ml for monotherapy and 800 to 2500 ug/ml for combined therapy
  - Collect sample after 2 hours of dosing
    - Avoid peak concentration

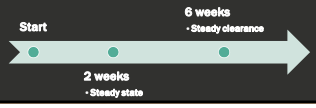


Primidone

Evidence level: I

Grade of Recommendation for Monitoring: A

- Pharmacology
  - Rapidly metabolized to its major active metabolite phenobarbital that is responsible for more than 85% of the total anticonvulsant activity
  - Similar pharmacokinetic profile as phenobarbital
- Panel recommendations
  - Initial dose of 10 mg/kg q 12 hours
  - Monitor levels at 2 and 6 weeks and every 6 months,
    - 2 weeks after a dose change or with increase in seizure frequency
  - Monitor if signs of toxicity
  - Patient therapeutic range of 15-35 ug/ml
  - Collect trough sample for dogs with recurrent seizures



Imepitoin

Evidence level: I

Grade of Recommendation: C

Approved in Europe

- Pharmacology
  - Elimination half-life of approximately 2 hours
  - No known therapeutic concentration
  - Low inter-individual metabolism variability
  - No indication of drug-drug interaction
- Panel recommendation:
  - Initial dose of 10-30 mg/kg q 12 hours
  - Drug monitoring is *not* recommended except in rare cases of concern for owner compliance

Levetiracetam

Evidence level: I

Grade of Recommendation for Monitoring: C

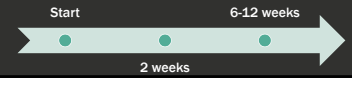
- Pharmacology
  - Elimination half-life
    - Monotherapy: 4-8 hours
    - With phenobarbital = 2-4 hours
  - Low hepatic metabolism
  - Low drug-drug interaction
- Panel recommendations:
  - Initial dose of 20 mg/kg q 8 hours
  - Monitoring is *not* routinely recommended
  - Monitoring may be indicated with concomitant phenobarbital treatment if satisfactory seizure control is not achieved.
    - Trough and Peak levels are most helpful

Zonisamide

Evidence level: II

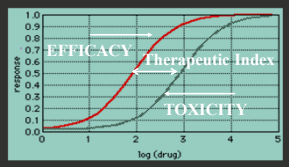
Grade of Recommendation for Monitoring: A

- Pharmacology
  - Elimination half-life of 15-20 hours
  - Hepatic metabolism but without hepatic autoinduction
  - Increased clearance with concomitant phenobarbital use
  - Weak carbonic anhydrase inhibitor
- Panel recommendations with the following criteria:
  - Initial dose
    - Monotherapy: 5 mg/kg q 12 hours
    - With phenobarbital : 10 mg/kg q 12 hours
  - Monitor levels at 2 weeks and then every 6 months,
    - 2 weeks after a dose change or with increase in seizure frequency
  - Collect trough time if used as monotherapy
  - Collect trough and peak (3 hours) if used with phenobarbital
  - Patient therapeutic range of 10-40 ug/ml



What Are The Risks Of Treatment?

- Type 1: *Predictable* and directly related to pharmacological effects in a dose dependent fashion
- Type 2: *Unpredictable* (idiosyncratic) and may be life-threatening
- Type 3: *Cumulative* effects with longer term therapy and may be life-threatening
- Type 4: *Delayed* consequences (carcinogenic/teratogenic) and life-threatening



	Type 1	Type 2	Type 3	Type 4
Phenobarbital	Behavioural changes	• Immune-mediated anemia, neutropenia or thrombocytopenia, • Acute, idiosyncratic hepatotoxic reactions • Superficial necrolytic dermatitis in dogs	• Psychogenic polydipsia with associated polyuria • Elevation of the serum alkaline phosphatase level • Factitious decrease in serum total and free thyroxine (T4) • Drug-induced hepatotoxicity (>35 ug/ml) • Physical dependence and associated withdrawal effects	Not reported
Potassium bromide	Increased lethargy and mild ataxia with increasing serum concentration	• Pancreatitis and gastrointestinal intolerance • Idiosyncratic allergic bronchitis • Panniculitis	• Polydipsia and polyphagia • Pelvic limb ataxia and weakness • Altered behaviour • Megaesophagus • Caution should be used when treating dogs with underlying renal insufficiency	Not reported
Primidone	Similar to Phenobarbital	Similar to phenobarbital	• Higher prevalence of hepatotoxicity than phenobarbital	Not reported
Imepitoin	• Somnolence/sedation • Polyphagia, polyuria and polydipsia • Hyperactivity • Ataxia	Not reported	None reported	Imepitoin is *not* genotoxic, teratogenic or immune toxic
Levetiracetam	Ataxia only parameter to differ from baseline	Not reported	Not reported	Not reported
Zonisamide	Sedation, ataxia and gastrointestinal upset	• KCS • Polyarthropathy • Acute toxic hepatic necrosis • Renal tubular acidosis	• Lower total T4 levels • Lower total CO2	Not reported

What is Drug-Resistant Epilepsy?

International League Against Epilepsy Task Force
Kwan et al, Epilepsia 52:1069-1077, 2010

Drug Treatment Success

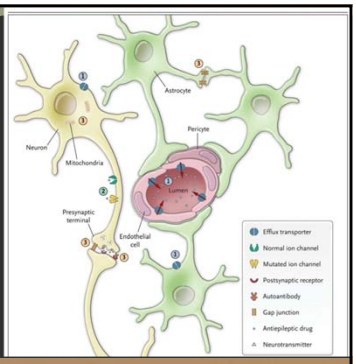
- Seizure free duration at least 3 times the longest seizure free period prior to onset of treatment
- Minimum duration of 12 months

Drug-Resistant Epilepsy

- Level 1
  - Undetermined outcome
    - Inadequate time or drug dose
  - Monotherapy failure
    - Continued seizure recurrence despite appropriate drug selection, time of treatment and serum concentration
- Level 2
  - Failure of adequate trials of 2 tolerated and appropriately chosen AEDs

What Causes Drug-Resistance?

- Transporter hypothesis (1)
  - Reduced AED CSF concentration
- Target hypothesis (2)
  - Decrease AED action at receptor
- Network hypothesis (3)
  - Altered connectivity
- Gene variant hypothesis
  - Genetic protein alteration
- Intrinsic severity hypothesis
  - High seizure density and/or frequency correlated with poorer prognosis



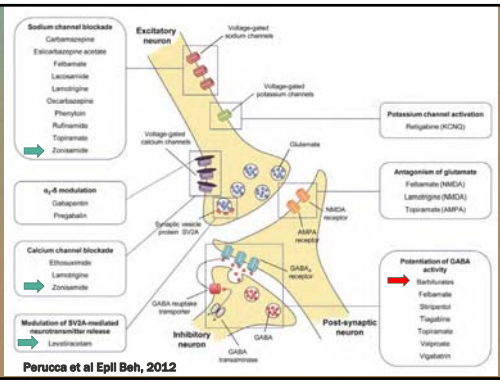
Kwan P et al. Drug-Resistant Epilepsy N Engl J Med 2011; 365:919-926

When Should a Second AED Be Started?

- Strict criteria for decision-making strategy on starting a second AED is lacking in veterinary medicine
- Risk factors associated with poorer seizure control include male dogs and prior cluster seizure activity
  - (Packer et al. 2014)
- Factors to consider
  - Selection of an AED with a different mechanism of action
  - Minimizing drug-drug interactions, avoiding additive toxicity
  - Determination of risk-benefit of polypharmacy versus quality of life

Panel Recommendations:

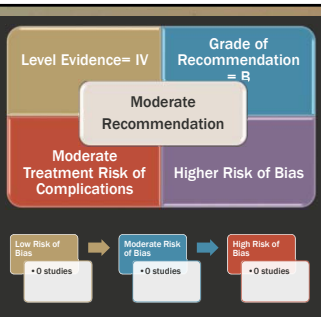
- Documentation of appropriate drug and maximal level of first AED for a minimum of 3 months
- > 50% increase in seizure frequency over 3 months
- New onset of status epilepticus
- New onset of cluster seizures
- Presence of drug-toxicity



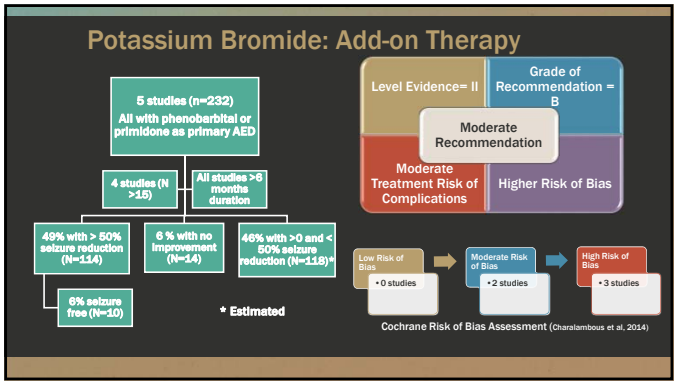
Perucca et al Epil Beh, 2012

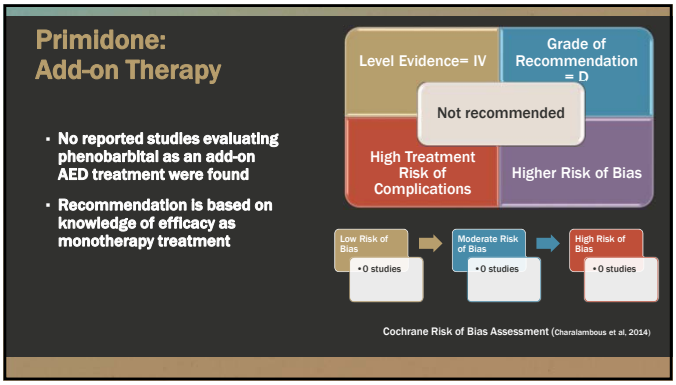
Phenobarbital: Add-on Therapy

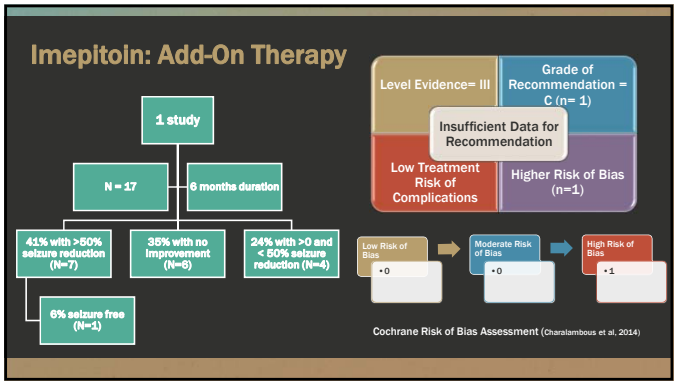
- No reported studies evaluating phenobarbital as an add-on AED treatment were found
- Recommendation is based on knowledge of efficacy as monotherapy treatment

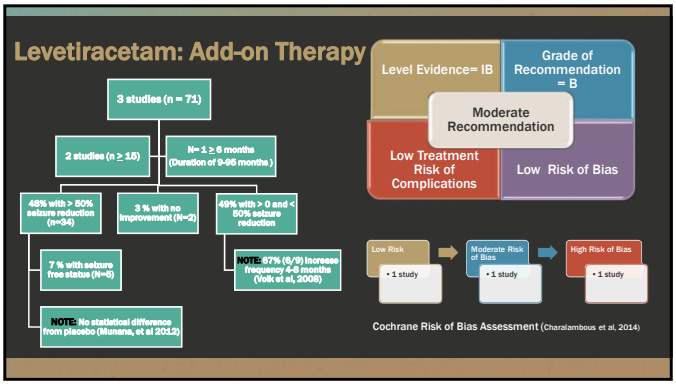


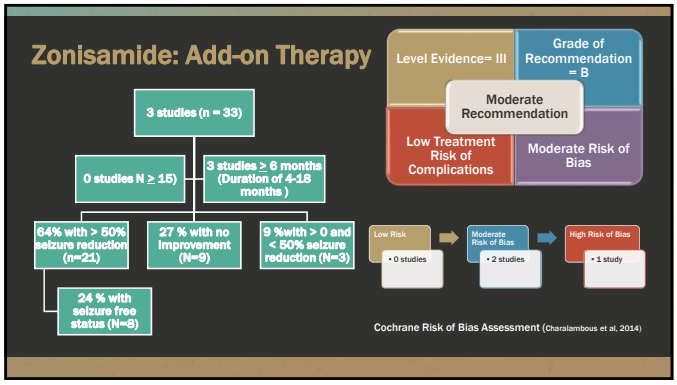
Cochrane Risk of Bias Assessment (Charalambous et al, 2014)











ACVIM Panel Add-on Therapy Recommendations:

DRUG	LEVEL OF EVIDENCE	GRADE OF RECOMMENDATION
Phenobarbital	IV	B
Bromide	II	B
Primidone	II	D
Imepitoin	III	C
Levetiracetam	IB	B
Zonisamide	III	B

ACVIM Panel Grade of Recommendations (Level of Evidence) for Add-On AED Therapy

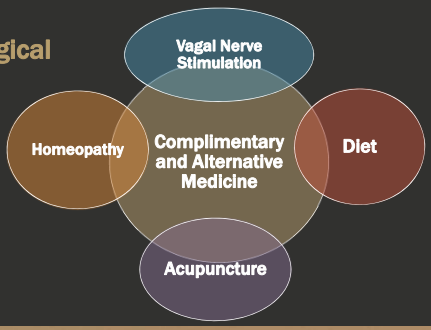
A (HIGH)	B (MODERATE)	C (LOW)	D (NO)
	• Levetiracetam (IB) • Bromide (II) • Zonisamide (III) • Phenobarbital (IV)	• Imepitoin (III)	• Primidone (II)

Additional AED Information for Use

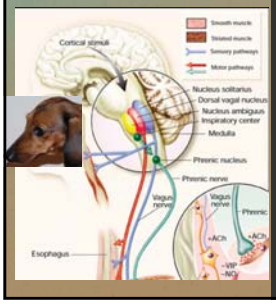
Insufficient Data For Treatment Recommendations

- **Felbamate**
  - 1 clinical study (N= 6) (III)
  - 6/6 with > 50% reduction for 6 months (CP seizures)
- **Gabapentin**
  - 2 clinical studies N=25 (III)
  - 11/25 with > 50% reduction for 3 or 4 months
- **Pregabalin**
  - 1 clinical study (n =9) (III)
  - 7/9 with > 50% reduction for 3 months
- **Topiramate**
  - 1 clinical study (n =10) (III)
  - 5/10 dogs with > 50% reduction for 6-15 months
- **Lacosamide**
  - No clinical studies
- **Rufinamide**
  - No clinical studies

What Alternative Non-Pharmacological Treatments Are Available?



Vagal Nerve Stimulation (VNS)



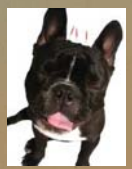
- Placebo-controlled, cross-over study evaluating the use of VNS in 10 dogs with medically refractory idiopathic epilepsy (Muñana et al, 2002)
- Treatment and control periods were both 13 weeks in duration
- No significant difference seizure frequency between groups over the total study time period
- Significant decrease in seizure frequency of 34% was detected with VNS for the final 4 weeks of treatment

Courtesy of Dr. Munana

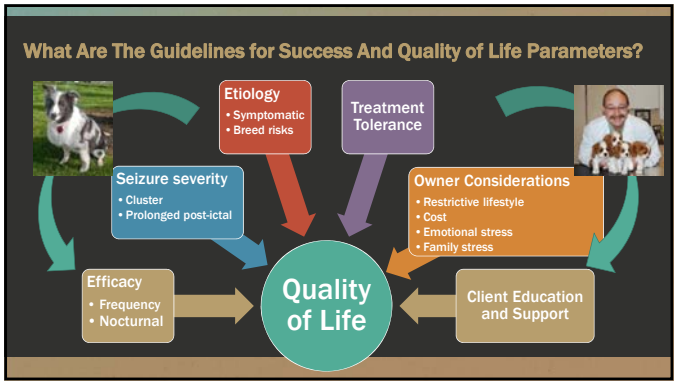
Diet

- **Ketogenic (MCT)**
  - Level of evidence: IB Insufficient Data to Recommend
  - Randomized placebo cross-over for 6 months (N=11)
    - Patterson et al, 2005
    - No difference in seizure control
    - 3 cases pancreatitis
  - Randomized, blinded placebo control for 3 months (N=21) (Law et al. 2015)
    - 7 with > 50% improvement
- **Fatty acid supplementation**
  - Level of evidence: IB Insufficient Data to Recommend
  - Single blinded randomized, placebo cross over for 3 months (N=15)
    - Matthews et al 2012
    - No difference in seizure control
- **Hypoallergenic**
  - Level of evidence: IV Insufficient Data to Recommend
  - One retrospective non-controlled study (abstract N =8) with report of improvement (Luján et al, 2004)

Eastern Based Alternative Therapy



- **Acupuncture (Gold Bead Implantation)**
  - Evidence level = III Insufficient Data for Recommendation
  - Overall decrease in mean seizure frequency of 38.7% (N= 15 with 7 on AED) for 15 weeks (Golz-Marquez et al, 2009)
- **Homeopathy**
  - Evidence level = III Insufficient Data for Recommendation
  - Belladonna +/- Cocculus 6C (N=10) for up to 8 months with variable degree of improvement (Varshney, 2007)



What We Accomplished

- Developed a working clinical consensus statement for canine seizure management
- Demonstrated that a collaborative international approach is achievable
- Established a predetermined, concise and logical sequential approach to seizure management
- Established a framework for future veterinary clinical and translational epilepsy treatment studies
- Revealed a great need for controlled clinical trials

International Veterinary League Against Epilepsy ?