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/

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, remote and loged 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. Which drug should be used second?
  4. How should AED monitoring be performed?
  5. What are the risks of treatment?
  6. What is drug-resistance?
- 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
- Web of Science (http://wok.mimas.ac.uk)
- CAB Abstracts (www.cabdirect.org)
- Web of Science (http://wok.mimas.ac.uk)

Studies included following modified criteria laid out in detail by Charalambous et al. 2014
- Any peer-reviewed study without language restrictions to which an antiepileptic drug was used and in dogs with epilepsy

Proceedings
- Annual Congresses of the European Society for Veterinary Neurology and the American College of Veterinary Internal Medicine

Evidence Type Of Evidence Grade Of Recommendation

Level Of Evidence
I Approximately designed, uncontrolled trials
II Randomised controlled trials
III Non-randomised controlled trials and drug efficacy of at least 50% seizure reduction for > 6 months
IV Published papers and proceedings

Type Of Evidence
- Clinical risk factors associated with AED responsiveness in canine epilepsy, 2014
- Charalambous et al. Treatment in canine epilepsy- a systematic review. BSAV Veterinary Research, 2014

Grade Of Recommendation
A High and likely to be effective
B Moderate and likely to be effective
C Low and may not be effective
D Not recommended

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
- ESET: “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**
- **Levetiracetam**
- **Zonisamide**

### Phenobarbital Monotherapy

- **Level Evidence = I**
- **Grade of Recommendation = A**
- **Moderate Treatment Risk of Complications**
- **Low Risk of Bias**
- 8 studies (n = 315)
- 82% with > 50% seizure reduction (N=255)
- 31% with seizure free status (N=96)
- 15% with no improvement (N=47)
- 3% with > 0 and < 50% seizure reduction (N=9)

### Potassium Bromide Monotherapy

- 1 study
- N = 23
- 74% with > 50% seizure reduction
- 16% with >0 and < 50% seizure reduction

### Primidone Monotherapy

- 6 studies (n = 103)
- 38% with > 50% seizure reduction (N=39)
- 35% with seizure free status (N=36)
- 21% with no improvement (N=22)
- 41% with > 0 and < 50% seizure reduction (N=42)

### Levetiracetam Monotherapy

- No published reports evaluating the use of levetiracetam as first line therapy in dogs with epilepsy

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**Dr Michael Podell   MedVet Chicago**
Zonisamide Monotherapy

- 1 study (n = 10)
  - 50% with > 50% seizure reduction
  - 50% with no improvement
  - 0% with > 0 and < 50% seizure reduction
  - 0% with seizure free status

Low Risk of Bias
- 0 studies

Moderate Risk of Bias
- 0 studies

High Risk of Bias
- 1 study

Level Evidence: III

Grade of Recommendation: C

Evidence level: I

Grade of Recommendation for Monitoring: A

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

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

ACVIM Panel Monotherapy Recommendations:

<table>
<thead>
<tr>
<th>DRUG</th>
<th>LEVEL OF EVIDENCE</th>
<th>GRADE OF RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Bromide</td>
<td>I</td>
<td>B</td>
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<tr>
<td>Primidone</td>
<td>II</td>
<td>D</td>
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<tr>
<td>Imepitoin</td>
<td>I</td>
<td>A</td>
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<tr>
<td>Levetiracetam</td>
<td>IV</td>
<td>C</td>
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<tr>
<td>Zonisamide</td>
<td>III</td>
<td>C</td>
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How Should AED Monitoring Be Performed?

- Objectives
  - Determine effective drug levels after initiation of successful therapy
  - Determine if drug failure is due to:
    - Pharmacokinetic factors to focus on a change in dose
    - Pharmacodynamic factors to focus on a change in drugs
  - 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

- **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 3.8 mg/kg q 12 hours
  - Monitor levels at 2 and 6 weeks and every 6 months and 2 weeks after a dose change or if increase in seizure frequency
  - Monitor 5 origins of toxicity
- **Patient therapeutic range** 55-38 µg/ml
  - Collect dose sample for dogs with recurrent seizures
  - Start
  - 2 weeks
  - steady state

Monitoring Schedule
Potassium Bromide

- **Pharmacology**
  - Elimination half-life 18-30 days
  - Renal elimination
  - No protein binding
- **Panel recommendations**
  - Initial dose or 30 to 60 mg/kg/day (single or divided)
  - Monitor at 6 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
  - Therapeutic panel range: Initial dose of 30 to 40 mg/kg/day (single or divided)
  - 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

- **Evidence level:** I
- **Grade of Recommendation:** A

Primidone

- **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
- **Evidence level:** I
- **Grade of Recommendation:** A

Imepitoin

- **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

- **Evidence level:** I
- **Grade of Recommendation:** C

Levetiracetam

- **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

- **Evidence level:** I
- **Grade of Recommendation for Monitoring:** C

Zonisamide

- **Pharmacology**
  - Elimination half-life of 15-20 hours
  - Hepatic metabolism but without hepatic autoinduction
  - Increased clearance with concurrent 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 and peak (3 hours) if used with phenobarbital
  - Patient therapeutic range of 10-40 ug/ml

- **Evidence level:** II
- **Grade of Recommendation for Monitoring:** A

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**  | Behavioral changes  | Toxicokinetic changes  | Renal/renal function changes  
• Deterioration motor function  
• Neuronal death in motor neurons  
• Demyelination of axons  
• Autonomic nerve function  
• Anoxic neuronal death  
• Superficial necrolytic dermatitis in dogs  
• Phagocytic death in associated animals  
• Reduction in axon sprouting  
• Increase in axon sprouting  
• Drug-related hepatotoxicity (90-94% Tt)  
• Physical disorders 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 behavior  
• 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  
• Hyperactivity  
• Ataxia  
• Not reported

**Levetiracetam**  | Ataxia only parameter to differ from baseline  
• 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

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**What is Drug-Resistant Epilepsy?**

International League Against Epilepsy Task Force
Kwan et al, Epilepsy 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 trial or drug dose
  - Microtherapy 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

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**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
- Intrinsic severity hypothesis
  - High seizure density and/or frequency correlated with poorer prognosis

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**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

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**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

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

- Low Risk of Bias
  - >5 studies
- Moderate Risk of Bias
  - >3 studies
- High Risk of Bias
  - >1 studies

**Characteristics of Bias Assessment (Charalambous et al, 2014)**

- Level Evidence= IV
- Grade of Recommendation = B

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Potassium Bromide: Add-on Therapy

- 5 studies (n=232)
- All with phenobarbital or primidone as primary AED
- 49% with > 50% seizure reduction (N=114)
- 6% seizure-free (N=10)
- 6% with no improvement (N=14)
- 46% with >0 and < 50% seizure reduction (N=118) *

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

Levetiracetam: Add-on Therapy

- Level Evidence= IB
- Grade of Recommendation = B
- Low Treatment Risk of Complications
- Low Risk of Bias

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

ACVIM Panel Add-on Therapy Recommendations:

- Phenobarbital: LEVEL OF EVIDENCE IV, GRADE OF RECOMMENDATION B
- Primidone: LEVEL OF EVIDENCE II, GRADE OF RECOMMENDATION D
- Zonisamide: LEVEL OF EVIDENCE III, GRADE OF RECOMMENDATION B
ACVIM Panel Grade of Recommendations (Level of Evidence) for Add-On AED Therapy

A (HIGH)
- Levetiracetam (IB)
- Bromide (II)
- Zonisamide (III)
- Phenobarbital (IV)

B (MODERATE)
- Imepitoin (III)
- Primidone (II)

C (LOW)
- Imepitoin (III)

D (NO)
- Primidone (II)

Additional AED Information for Use

Insufficient Data For Treatment Recommendations

What Alternative Non-Pharmacological Treatments Are Available?

Vagal Nerve Stimulation
Complimentary and Alternative Medicine
Diet

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 in 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

Diet
- Ketogenic (MCT)
- Level of evidence: IB
- Insufficient Data to Recommend
- Randomized placebo cross-over for 6 months (Muñana et al, 2002)
  - No difference in seizure control

- Fatty acid supplementation
- Level of evidence: IB
- Insufficient Data to Recommend
- Single blinded randomized placebo cross-over for 6 months (Matthews et al, 2012)
  - No difference in seizure control

- Hypoallergenic
- Level of evidence: IV
- Insufficient Data to Recommend
- One retrospective non-controlled study showed no statistically significant 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=25 with 7 on AED) for 15 weeks (Goiz-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 (Hontoria, 2007)
What Are The Guidelines for Success And Quality of Life Parameters?

- Efficacy
  - Frequency
  - Nocturnal

- Seizure severity
  - Cluster
  - Prolonged post-ictal

- Etiology
  - Symptomatic
  - Breed risks

- Treatment Tolerance

- Owner Considerations
  - Restrictive lifestyle
  - Cost
  - Emotional stress
  - Family stress

- Client Education and Support

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?