
ALMA MATER STUDIORUM
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MYLAV
Laboratorio La Vallonea
"Clinical and therapeutic approach to the idiopathic epileptic dog"

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"Clinical and therapeutic approach
to the idiopathic epileptic dog "
... what's the best way to tell the whole story?

2


«Consensus statement»
Guidelines published by a group of acknowledged experts
aimed to standardize the approach to a specific problem

3

in these last years….


Journal of Veterinary Internal Medicine

ACVIM Consensus Statement

2015 ACVIM Small Animal Consensus Statement on Seizure Management in Dogs


CORRESPONDENCE

Open Access

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


CORRESPONDENCE

Open Access

International veterinary epilepsy task force consensus proposal: outcome of therapeutic interventions in canine and feline epilepsy

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Goal of the lecture:

Provide a comprehensive and rational clinical approach to the idiopathic epileptic dog

INDEX:

1. The owner's perspective
2. What is Epilepsy?
3. What happens during a seizure?
4. Idiopathic or structural Epilepsy?
5. Goals of the treatment?
6. When starting treatment?
7. Which drug should I use first?
8. It is not doing well … what can I do?

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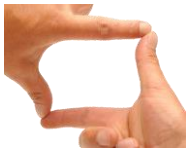
1.



The owner's perspective

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…. The owner's perspective ….

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…. My examination….

30%
The neurological examination

70%
Explanation to the owner

- What is Epilepsy
- How to reach the diagnosis
- What does it mean *"treating epilepsy"*

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The owner and the management of epilepsy

Taylor ⟷ Clothes factory

9

2.

What is Epilepsy?

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DEFINITIONS

Epilepsy: from Greek "epilambanein" (being attacked,, possessed), referred to people affected by the "holy disease"

"Epilepsy" – chronic brain disorder characterized by the recurrence of epileptic seizures" (Fisher et al., 2005)

"Epileptic Seizure" is the transient manifestation of clinical signs reflecting an abnormal, excessive and/or hypersinchronous neuronal electrical activity in the brain" (Fisher et al., 2005)

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Classification of Seizures :

According to the frequency

- Single seizure
  (interval more than 24 h)
- Cluster of seizures
  (interval less than 24h)
- Status Epilepticus
  (seizures lasting more than 5 minutes or 2 or more seizures in 30 minutes without full recovery)

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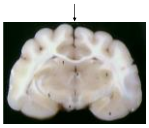
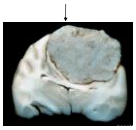
Epilepsy

IDIOPATHIC



- Genetic
- Suspected genetic
- Of unknown origin

STRUCTURAL



- Neoplasia
- Inflammatory/infectious
- Cerebrovascular accidents
- Anomalies
- Degenerative disorders
- Trauma
- Metabolic disorders?

reactive seizures

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Idiopathic Epilepsy

Aetiology ???

- Genetic
- Suspected genetic
- Of Unknown origin

Idiopathic Epilepsy in the dog is most probably a genetic hereditary disease

"CHANNELOPATHY"

The diagnosis of Idiopathic Epilepsy is "by exclusion"

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Idiopathic Epilepsy

DIAGNOSIS:

International Veterinary Epilepsy Task Force (2015)

Tier I confidence level:

- History of > 2 epileptic seizures
- Age between six months and six years
- Normal neurological examination
- CBC, Blood profile and urinalysis normal

Tier II confidence level:

- Tier I prerequisite
- Normal pre- e post prandial bile acids
- Normal advanced diagnostic imaging (CT or MRI)
- Normal cerebrospinal fluid (CSF) examination

Tier III confidence level:

- Tier II prerequisite
- EEG tracing compatible with Epilepsy

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3.

What happens during a seizure?

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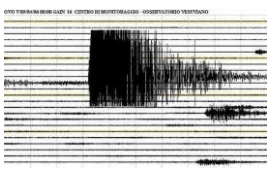
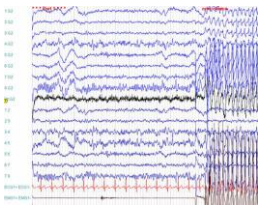
An earthquake



An epileptic seizure



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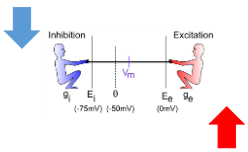
Physiopathology

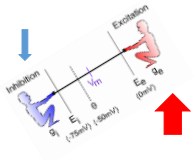
INHIBITION

EXCITATION

NORMAL BRAIN



EPILEPTIC BRAIN



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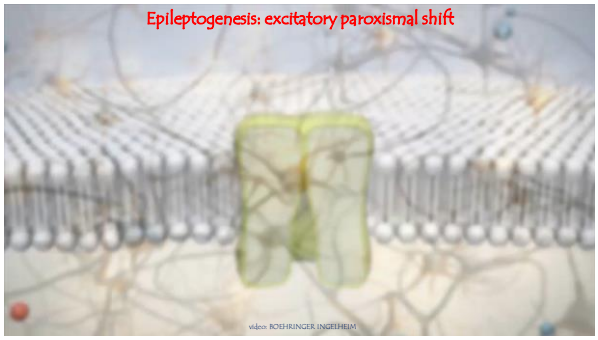

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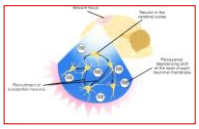
Physiopathology

- Abnormal hypersinchronous activity
- Imbalance between excitatory and inhibitory systems
- Lack of adequate inhibitory feed-back



Propagation

Epileptic seizure!

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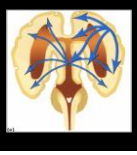
Classification of epileptic seizures

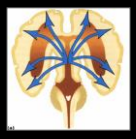
According to the clinical presentation

FOCAL

FOCAL with secondary generalization



GENERALIZED



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Focal seizure

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Focal seizure

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Generalized tonic-clonic seizure

3 Phases :

- Prodromal Phase
- (Aura) Ictal phase
- Post-ictal phase

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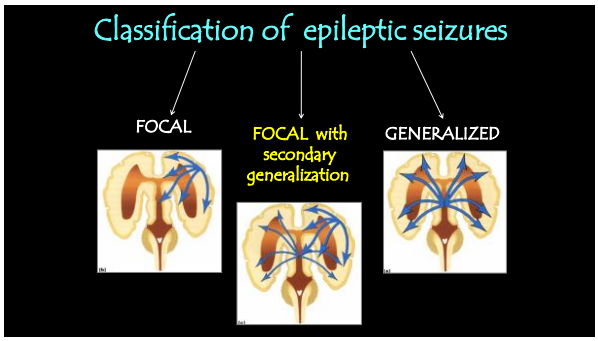
Classification of epileptic seizures
FOCAL
FOCAL with secondary generalization
GENERALIZED

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Focal onset («Aura»)

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«secondary generalization»

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Post-ictal phase

Variable duration: → few minutes to several hours

Neurologic Signs due to neuronal exhaustion
(cell damage due to hypoxia, acidosis and failure of the membrane pumps)

- Amaurosis (central blindness)
- Ataxia
- Disorientation
- Polyphagia
- Vomiting
- Temporary various neurological deficits

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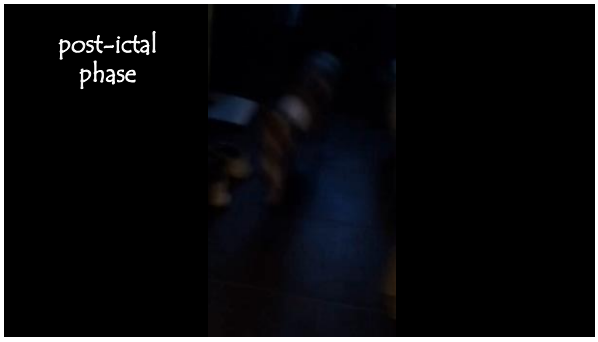

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4.

Idiopathic or Structural epilepsy?

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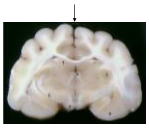
Epilepsy

IDIOPATHIC



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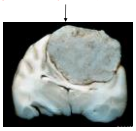

- Neoplasia
- Inflammatory/infectious
- Cerebrovascular accidents
- Anomalies
- Degenerative disorders
- Trauma
- Metabolic disorders?

reactive seizures

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Algorithm of the priorities

1 Epileptic seizure or Syncope???

Examination of cardiovascular, respiratory and NERVOUS systems

2 Idiopathic or secondary Epilepsy??

Examination NERVOUS system, diagnostic work-up

3a Idiopathic Epilepsy → SPECIFIC THERAPY

3b Secondary Epilepsy → diagnostic work-up, advanced imaging → 4 STRUCTURAL / REACTIVE SEIZURES

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PHYSICAL EXAMINATION

Idiopathic or Secondary Epilepsy?

NEUROLOGICAL EXAMINATION!!!
(after at least 48 hours from the last seizure)

NORMAL → IDIOPATHIC EPILEPSY (majority of cases)

NEUROLOGIC DEFICITS → STRUCTURAL EPILEPSY (or reactive seizures)

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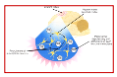
PHYSICAL EXAMINATION

Scenario: NEUROLOGIC DEFICITS

"short cut":

EPILEPTIC SEIZURE



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CEREBRAL CORTEX

↓

FOREBRAIN

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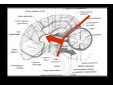
Forebrain syndrome



POSSIBLE CLINICAL SIGNS:

Seizures and…

- behavioural abnormalities
- Gait ± normal
- Menace response deficit
- Proprioceptive deficits

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An example to summarize

"ARTU'", BOXER, m, 5y, 31kg

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"ARTU'", BOXER, m, 5y, 31kg

HISTORY

- Artù was referred because since approximately THREE MONTHS is experiencing generalized tonic-clonic seizures
- Seizures had an initial frequency of one every 15 days, and, in the last month, one per week.
- the referring vet prescribed Phenobarbital 3 mg/kg Bid, stopped by the owner after ten days due to the excessive sedation of the dog
- Artù has a normal vaccination plan, is on pet food diet and lives in urban environment.

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"ARTU'", BOXER, m, 5y, 31kg

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"ARTU'", BOXER, m, 5y, 31kg

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"ARTU'", BOXER, m, 5y, 31kg

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"ARTU'", BOXER, m, 5y, 31kg

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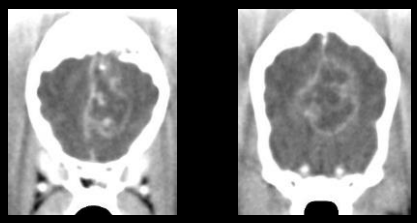
"ARTU'", BOXER, m, 5y, 31kg



CT: suspected forebrain GLIOMA

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Clinical differential diagnoses

V Vascular
I Inflammatory/infectious
T Trauma
A Anomalous (Congenital)
M Metabolic
I Idiopathic
N Neoplastic
D Degenerative

CVA, Ischemia, Hemorrhage

Distemper, **MUE**, Abscess

Hydrocephalus, cortical dysplasia, porencephaly

Hypoglycemia, Hypocalcemia, Hepatic Encephalopathy

Primary and secondary tumors

Organic Aciduria, storage diseases

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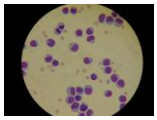
Diagnostic Work-up

- ✓ CBC & ematobiochemical profile
- ✓ bile acids & blood ammonia
- ✓ thorax X-ray/abdominal US
- ✓ ADVANCED DIAGNOSTIC IMAGING
  - Computed Tomography (CT)
  - Magnetic Resonance Imaging (MRI)
- ✓ Cerebrospinal fluid exam



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Everything ok?

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*Take home message

- Epilepsy: different severity and phenotype! ...«umbrella»...
- You and the owner are the same team:
  GOOD COMMUNICATION: make him aware of what Epilepsy is in term of expectations, limitations, necessity of periodic controls
- Pathogenesis → inbalance between excitatory and inhibitory mechanisms
- Type of seizures: focal and generalized
- Idiopatic and structural Epilepsy
- structural Epilepsy: epileptic seizures and forebrain signs
  Behavioural abnormalities
  Proprioceptive deficits
  Abnormal menace response
- Complete diagnostic work-up

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5.

Goals of the treatment?

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General principles and goals

- GOAL:: REDUCTION (not elimination!!!) of the frequency and severity of the seizures
- Chronic therapy maintained for the whole life of the patient and possible relevant side-effects
- Clear and complete communication with the owner:
  - . realistic expectations on therapeutic effects
  - . awareness of possible side effects
  - . Necessity of periodic medical control

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Epilepsy treatment

Tailor ⟷ Clothes factory

PRIORITIES:

FIRST: Control Seizures
SECOND: Control Side-effects

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When Should Treatment Be Started?

The decision to start AED treatment is based on a number of factors, including etiology, risk of recurrence, seizure type, tolerability, and adverse effects. Risk factors for seizure recurrence are not well established for cats and dogs. A number of relative risk factors

When should treatment be started?

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When should treatment be started?

- Not possible to produce "cooking recipes"
- Normally treatment is started:
  - after that the diagnostic work up has excluded other causes;
  - after the confirmation of the recurrence of the seizures (at least 2 in 6 months);
  - immediately, in case of :
    - cluster seizures /status epilepticus
    - Structural epilepsy
- Choice of the drug and dosage depends upon the aggressiveness of epilepsy
  Consider: costs and potential side effects

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Which Drug Should Be Used First?

Selection of AED is based on a number of factors, including seizure type, efficacy, and tolerability. No evidence exists that any single AED provides a better outcome for adults with unprovoked epilepsy when early treatment is started in people.[18] Drug selection, therefore, is often based on tolerability in both people and dogs. The panel recommendations are summarized in Table 1.

Which drug should I use first?

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Which drug should be used first?

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

Drug	Monotherapy recommendation Level	Monotherapy recommendation Grade
Phenobarbital	I	A
Bromide	I	B
Primidone	II	D
Imepitoin	I	A
Levetiracetam	IV	C
Zonisamide	III	C

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

Phenobarbital and Imepitoin

"High recommendation and likely be effective treatment, appropriately designed, controlled trials"

Bromide

"Moderate recommendation and most likely to be effective treatment"

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Phenobarbital

First- line drug in the treatment of Epilepsy in the dog

MECHANISM of ACTION:

Enhances the mechanisms of hyperpolarization and the stability of the cell membranes

PHARMACOKINETICS

Liposoluble drug well absorbed ater IV, IM and oral administration;
Metabolized in the liver → NO induction of liver enzymes!
Half life time ~ 50 hours
"Steady state" ~ 15-20 days

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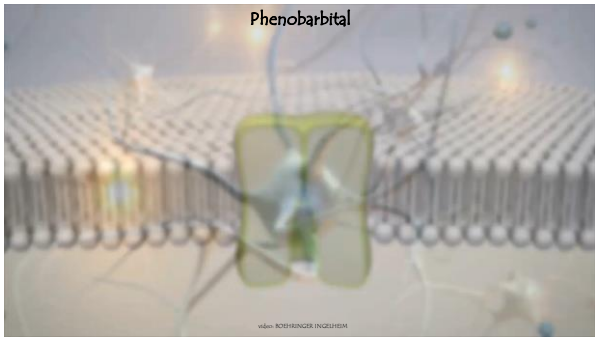

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Phenobarbital

DOSAGE

Initial dosage: 2,5 mg/kg PO BID

Monitoring plasma levels after two-three weeks:
(therapeutic range 15-35 µgr/ml)

SIDE EFFECTS

Polyphagia
Polyuria/Polydipsia
Sedation
Ataxia
Hepatotoxicity???

Normally not recorded under 35 µg/ml in healthy dogs

Check periodically (every 6 months) the liver function (test ALT, AST, SAP, Bile acids, albumin, Cholesterol)

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Imepitoin

First AED developed in veterinary medicine for the treatment of canine Epilepsy

Strenghts :

- Same efficacy as Phenobarbital
- less adverse effects

Weakness:

- COST!

MECHANISM of ACTION:

Partial agonist acting at the benzodiazepine recognition site of the $GABA_A$ receptor

PHARMACOKINETICS:

short half-life time (~ 2 hours)
Steady state achieved in ~ 2 days
metabolized by liver (oxidation)

DOSAGE: 10-30 mg/kg BID

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Imepitoin

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It is not doing well … what can I do?

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Therapeutic failure

No benefit or
seizures reduction frequency less than 50%

1. Wrong diagnosis:
   1. signalment? History?
   2. neurological examination?
   3. complete work-up?
2. Poor owner compliance:
   1. goals: good communication?
   2. wrong expectations?
   3. drug regimen (i.e. TID)?
   4. ….Just a bad owner…

- Refractory epilepsy
- Inappropriate dosages

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Therapeutic failure

No benefit or
seizures reduction frequency less than 50%

what's the next step?

- MONITOR SERUM LEVELS (if on PB or Bromide treatment)
- increase the dosage
  (depending on serum levels and side effects)
- think to associate another drug (and ask for the specialist advice)

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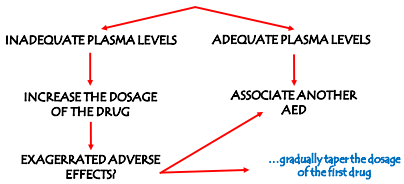
Therapeutic failure

WHAT CAN I DO?
(scenario «Phenobarbital»)

Inadequate dosage / inefficacy of the drug
monitor the plasma levels of the drug (PB : 15-35 µg/ml)



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Therapeutic failure

WHAT CAN I DO?

(scenario «Imepitoin»)

Inadequate dosage / inefficacy of the drug

↓

INADEQUATE DOSAGE (i.e. 10 mg/kg BID)

↓

INCREASE THE DOSAGE (20 mg/kg BID) → Seizures control → continue the treatment

INCREASE THE DOSAGE (20 mg/kg BID) → inadequate seizures control → INCREASE THE DOSAGE (30 mg/kg BID) → inadequate seizures control → ASSOCIATE ANOTHER AED

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Table 2. Qualified criteria recommendations for AED drug use.

Drug	Indications: Seizure type	Indications: Seizure etiology	Indications: Other	Drug monitoring	Cautions and risks	Initial dose
Phenobarbital				2 and 6 weeks, qtm, or	Hepatotoxicity	2.5 mg/kg q12h
Monotherapy	All	All		2 weeks after dose change;	Idiosyncratic blood dyscrasia	
Add-on	All	All		Range: 15–35 µg/mL	Necrolytic dermatitis	
				Increases clearance of levetiracetam and zonisamide		
Potassium Bromide				1 and 3 months, q12m or 1 month after dose change	Pancreatitis Sedation	40 mg/kg/day
Monotherapy	All	Idiopathic	Low initial frequency	Range: 1000–3000 mcg/mL (mono) or 800–2500 mcg/mL with phenobarbital	Ataxia	
Add-on	All	All	Liver disease			
Imepitoin						
Monotherapy	All	Idiopathic		NR		15 mg/kg q12h
Add-on	NR	NR				
Levetiracetam						
Monotherapy	All	All	Liver disease	NR	Renal disease	20 mg/kg q8h
Add-on	All	All				
Zonisamide				2 and 3 months, qtm and 2 weeks after dose change	Idiosyncratic renal and hepatic disease	5 mg/kg q12h
Monotherapy	All	All				7–10 mg/kg q12h with phenobarbital
Add-on	All	All		Range: 10–40 mcg/mL		

NR = not recommended.

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Second-line AEDs

Kalium Bromide

AED used in human medicine in the last century and then abandoned for its side effects on libido

Since the'80 used associated to Phenobarbital in refractory epilepsies or in hepatopatic patients.

MECHANISM of ACTION

Non completely understood. Apparently Br ions are more effective than Cl in the neuron cell membrane hyperpolarization

PHARMACOKINETICS

Very long half-life time (20-28 days); *Steady-state* achieved after 2-3 months

Eliminated by *kidneys* - NOT metabolized by the liver

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Second-line AEDs

Kalium Bromide

DOSAGE

Initial dosage: 20-40 mg/kg day PO

Monitoring plasma levels after two-three months:
(therapeutic range 1 – 3 mgr/ml)

SIDE EFFECTS

Polyphagia
Polyuria/Polydipsia
Sedation
Ataxia
Acute pancreatitis???

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Levetiracetam

. Approved by FDA in 1999
. Very well tolerated in human beings;
. Very effective in treatment of human refractory epilepsy;
. Different mechanism of action: Binds to synaptic vesicle protein (SV2A), influencing presynaptic neurotransmitter release
. Minimal hepatic metabolism → 70-90% excreted unchanged in urines
. Monotherapy at the same dosage
. Cats: dosage: 20 mg/kg TID per os
. Expensive

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.... Wrong Localization.....

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*Take home message

- Therapy: when to start treatment?
- No cooking recipes – «tailoring» according to each patient
- «Consensus»: Phenobarbital and Imepitoin first line drugs
- Before changing the drug be sure it is NOT working!
  check Phenobarbitalemia and Bromuremia
  use the AED till the highest dosage
- Second line drug: Bromide and Levetiracetam
- Excessive adverse effects – priorities :
  FIRST: control seizures
  SECOND: control side effects

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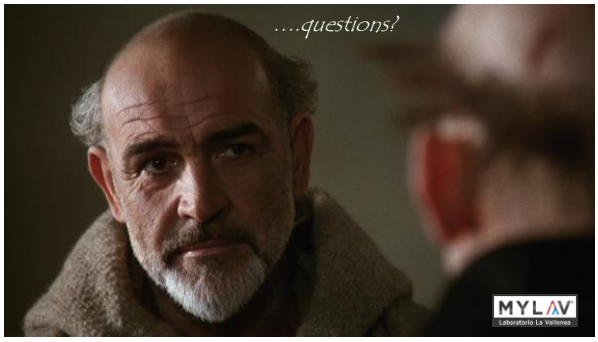

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