

Seizures and Anticonvulsants

- Seizure disorders are common in dogs and cats
 - Seizures occur more frequently in dogs than in cats
 - Lack of prevalence or incidence data
- A seizure is the clinical manifestation of a paroxysmal cerebral disorder
 - Caused by a synchronous and excessive electrical neuronal discharge
 - Originating from the cerebral cortex
- Cluster seizures are two or more seizures within a 24-hour period
- Status epilepticus is continuous seizures, or two or more discrete seizures between which there is incomplete recovery of consciousness, lasting at least 5 minutes
- Epilepsy is recurrent seizures of any type resulting from an intracranial cause

- True epilepsy originates from a nonprogressive intracranial disorder
 - Inherited epilepsy is caused by a genetically determined intracranial disorder
 - Acquired epilepsy is caused by a previously active intracranial disorder that is no longer active
 - Idiopathic epilepsy is a seizure disorder in which the cause and mechanism for the seizures is unknown
- Symptomatic epilepsy is caused by progressive intracranial disease

- Classification

- Based on clinical observations rather than EEG characteristics
- Partial seizures originate from a focus in one cerebral hemisphere and usually manifest localized clinical signs
- In animals, partial motor seizures are indicative of a lesion in the contralateral cerebral hemisphere (e.g., a left thoracic limb seizure indicates a right cerebral cortex lesion)
- Partial seizures are invariably acquired -> primary generalized epilepsy is not considered in the differential diagnosis

- Simple partial seizures

- No alteration in consciousness, and the clinical signs during the seizure are limited to isolated muscle groups (e.g., tonus or clonus of a limb)

- Complex partial seizures

- Accompanied by an alteration in consciousness
- There may be involuntary or compulsive actions such as chewing, licking, and defensive or aggressive behavior, hysteria, rage, autonomic reactions such as salivation, and hallucinations such as fly biting
- AKA psychomotor seizures

Genetic Factor Proved or Highly Suspected
Beagle
Dachshund
German shepherd dog (Alsatian)
Horak's laboratory dog
Keeshond
Belgian tervuren
Aberdeen Angus cattle
Brown Swiss cattle
Swedish Red cattle
High Incidence of Seizure Disorders
Arabian foal
Boxer
Cocker spaniel
Collie
Golden retriever
Irish setter
Labrador retriever
Miniature schnauzer
Poodle
Saint Bernard
Siberian husky
Wire fox terrier

- Animal falls and becomes unconscious, the limbs are extended rigidly, opisthotonos is usual, and respiration stops
 - Tonic phase is usually brief (10 to 30 seconds) and is rapidly followed by clonic limb movements in the form of running or paddling
 - Chewing movements of the mouth are common
 - Autonomic activity may start in the tonic or clonic phase of the ictus and may include pupillary dilation, salivation, urination, defecation, and piloerection
 - The clonic phase may alternate with tonic activity
 - Generalized tonic-clonic seizures in cats can be violent
 - Cats may be propelled into the air, and self-inflicted trauma may occur (contusions, excoriations, avulsion of nails, and biting the tongue)
 - Mild generalized seizures in cats are characterized by pupillary dilation, facial twitching, and, less frequently, salivation and urination
- Postictal phase: after the seizure
 - Animal may return to normal in seconds to minutes or may be restless, lethargic, confused, disoriented, or blind for minutes to hours
- The aura and the postictal phase do not have any relationship to the severity or the cause of the seizures
- It is important to know whether the seizure starts as generalized, symmetric activity or if it has a focal component
 - Do not confuse the aura with focal seizure activity
 - Any indication of focal motor activity preceding the generalized seizure, such as chewing, forced turning of the head, or clonic jerks of muscle groups, indicates a focal component, even if it generalizes secondarily
 - Primary generalized seizures cannot be localized anatomically
 - Whether the seizure focus is single or multiple, the generalized signs preclude localization
- Absences, or petit mal seizures, either are very uncommon in animals or, more likely, are not easily recognized
 - Characterized by a brief (seconds) loss of contact with the environment that occurs without motor activity
 - Variations in humans include minor motor components such as facial twitching, loss of postural tone, and autonomic activity
- Pathophysiology
 - Seizures are always a sign of abnormal forebrain function
 - Primary lesion in the brain or secondary to a metabolic abnormality
 - At the cellular level, seizures represent abnormal hypersynchronous discharges of cortical neurons
 - An imbalance exists between excitatory and inhibitory mechanisms that favor the sudden onset of excitation

- Several neurotransmitters play fundamental roles in the pathogenesis of seizures: GABA (inhibitory) and glutamate (excitatory) neurotransmitter agents
- Increased excitability of neurons may follow defects in inhibition or result from conditions or factors that directly promote neuronal excitation
- Kindling: each time a seizure discharge spreads, it increases the probability that it will spread again
 - Can be suppressed with appropriate anticonvulsant therapy
- The normal brain is capable of seizures in response to a variety of intracranial and extracranial stimuli
- When the brain's homeostasis is overcome, cerebrocortical excitability is altered and the seizure threshold is decreased
- Normal animals with a low seizure threshold may be induced to have a seizure by many factors
 - Fatigue, fever, estrus, photic stimulation
- Following establishment of a focal seizure focus, abnormal electrical activity may be recorded over the contralateral cerebral cortex -> secondary seizure focus 'mirror focus'
- Either the primary or secondary focus, or both, may cause seizures
- SE: failure of the normal brain homeostasis mechanisms that work to stop seizures
 - Dt persistent neuronal excitation, inadequate neuronal inhibition, or both
 - Extrasynaptic factors may be important in spreading and maintaining the seizure
 - Excess of excitatory neurotransmitters such as glutamate, aspartate, or acetylcholine, or GABA antagonists
 - SE lasting 30 to 45 minutes results in brain injury in experimental animals
 - Probably occurs in clinical patients after a much shorter time
 - May cause neuronal necrosis, particularly in brain regions with high metabolic rates
 - Early SE: protective increase in cerebral blood flow
 - Late SE: cerebral blood flow decreases simultaneously as blood pressure decreases, and cerebral metabolic rate (e.g., glucose and oxygen utilization) increases
 - Leads to ATP depletion and lactate accumulation -> neuronal necrosis
 - SE may be associated with systemic problems including hypoxemia, hyperthermia, aspiration pneumonia, systemic lactic acidosis, hyperkalemia, hypoglycemia, shock, cardiac arrhythmias, neurogenic pulmonary edema, and acute renal failure
 - Causes of SE
 - Toxicities or metabolic abnormalities
 - Sudden withdrawal of anticonvulsant medications
 - Ineffective anticonvulsant medications

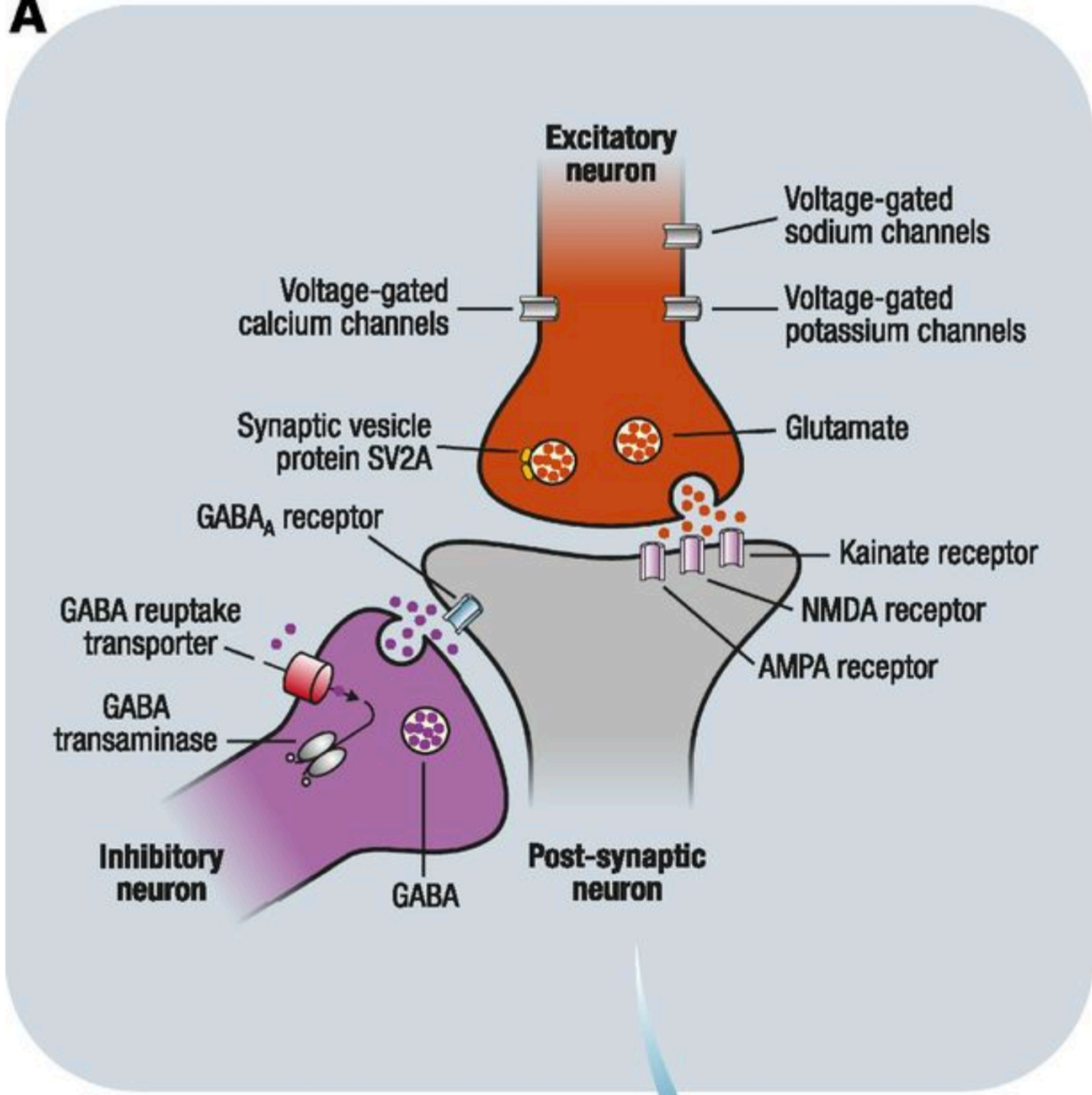
- Progressive brain diseases
 - The risk factors for development of SE have been studied in dogs with primary epilepsy
 - Dogs weighing 28.9 kg (63.6 lbs) or more were at increased risk compared with dogs weighing 17.4 kg (28.3 lbs) or less
 - One or more episodes of SE were predictive of future attacks
 - Mean life span of dogs with SE was 8.3 years compared with 11.3 years in epileptic dogs with no history of SE
 - Animals with SE may develop permanent brain damage and become refractory to anticonvulsant drugs
 - During severe seizures like those that occur in SE, transient brain hypoxia can occur
 - Hypoxia can produce central laminar necrosis and may result in permanent neurologic signs such as cortical blindness and mental retardation
 - Hyperthermia, commonly present in dogs with SE, enhances neuronal swelling and cerebral edema
 - Treatment for cerebral edema with mannitol and glucocorticoid steroids may be useful in some cases
- Etiology
 - Extracranial
 - Originating outside the body (toxins)
 - Originating within the body but outside the nervous system (liver disease)
 - Extracranial causes may result in generalized seizures, because they affect the brain globally
 - Intracranial
 - **Progressive:** inflammation (e.g., granulomatous meningoencephalitis), neoplasia, nutritional alterations (e.g., thiamine deficiency), infection, anomalous entities (e.g., hydrocephalus), and trauma
 - Most animals with progressive intracranial disease are clinically abnormal between seizures and usually have progression of clinical signs. However, seizures may be the only clinical sign for a prolonged time, before others become apparent.
 - **Nonprogressive:**
 - Inherited epilepsy (dogs): usually are 6 months to 5 years of age
 - Idiopathic epilepsy (dogs): 1-5y

Classification	Most Frequent Causes	Diagnostic Tests
Degenerative (15)	Storage diseases	Breed, biopsy
Anomalies (12)	Hydrocephalus	PE, CT, EEG, ventriculography
	Lissencephaly	Breed, PE, EEG
Idiopathic (13)	Genetic	Breed, age, history
	Unknown	Absence of other causes
Inflammation/infectious (15)	Viral: canine distemper, rabies, FIP	History, PE, CSF analysis, CSF titers
	Bacterial: any type	
	Mycotic: cryptococcosis	
	Protozoal: toxoplasmosis, neosporosis	
	Rickettsial: RMSF, ehrlichiosis	
	Granulomatous meningoencephalitis	
	Immune meningoencephalitis	
	Nonsuppurative encephalitis (cats)	
Metabolic (15)	Electrolyte: hypocalcemia	CBC, biochemical profile, UA, free bile acids, glucose-insulin pairs, hepatic biopsy
	Carbohydrate: hypoglycemia	
	Renal failure	
	Hepatic failure, portacaval shunt, microvascular dysplasia	
Neoplastic (15)	Primary: gliomas, meningiomas	NE, CT, MRI
	Metastatic	
Nutritional (15)	Thiamine deficiency	History, response to treatment
Toxic (15)	Heavy metal: lead	History, blood lead levels
	Organophosphates	History, NE, cholinesterase levels
	Chlorinated hydrocarbons	History, NE, PE
	Strychnine	
	Tetanus	
	Toad poisoning	
	5-hydroxytryptophan	
Traumatic (13)	Acute: immediately after head injury	History, PE, NE, CT, MRI
	Chronic: weeks to years after head injury	History, EEG, CT, MRI
Vascular (12, 13)	Infarctions	History, NE, CT
	Arrhythmias	Auscultation, ECG
Modified from Oliver JE Jr: Seizure disorders in companion animals, <i>Compend Cont Educ Pract Vet</i> 2:77-86, 1980.		
CBC, Complete blood cell count; CSF, cerebrospinal fluid; CT, computed tomography; ECG, electrocardiogram; EEG, electroencephalography; FIP, feline infectious peritonitis; MRI, magnetic resonance imaging; NE, neurologic examination; PE, physical examination; RMSF, Rocky Mountain spotted fever; UA, urinalysis.		

- Plan for management
 - One isolated seizure
 - PE and neuro exam
 - >1 seizure
 - Minimum database
 - 1: a definitive diagnosis
 - 2: a possible cause of the seizures that requires further tests to confirm
 - 3: no suggestion of the cause
 - When to treat
 - Generally recc'd when single seizures occur more than once every 6 weeks and when cluster seizures occur
 - Failure to control the seizures after adequate therapy warrants a complete database to rule out neurologic disease
 - Any change in neurologic signs also indicates a complete evaluation
 - Dogs older than 5 years of age or cats of any age most likely have an acquired disease
 - Brain tumors must be high on the list of rule-outs in all older animals, even when no neurologic signs are present
 - The safest and most accurate method of diagnosis is CT or MRI, and is recc'd for all these animals
 - If the findings are negative, CSF analysis and EEG should be done
 - Some breeds have primary generalized epilepsy that is difficult to control
 - German shepherd dogs, Saint Bernards, Labrador retrievers, and Irish setters
 - Negative findings on the complete database for an animal that has been poorly controlled with adequate anticonvulsant medication suggest a poor prognosis
 - Treatment can be altered by changing the dosage or the drugs, by combining drugs, or by changing the schedule of administration
 - Periodic reevaluation may reveal a progressive disease that was missed originally
- Plans for treatment
 - Successful treatment depends heavily on client education and cooperation
 - Treatment failures are usually the result of
 - Progressive disease
 - Refractory epilepsy
 - Inadequate client education or poor client compliance leading to subtherapeutic drug concentrations
 - Clients need to understand the importance of therapeutic drug monitoring to successful seizure management
 - Successful treatment may be manifested by
 - A reduction in the frequency of seizures

- A reduction in the duration of seizures
 - A reduction in the severity of seizures
- Strategies of antiepileptic drug therapy
 - Modulate membrane action of GABA****
 - Reduce excitatory transmission
 - Modulate membrane cation conductance

A



- Phenobarbital

- Exact mechanisms for the CNS effects caused by barbiturates are unknown, they have been shown to inhibit the release of acetylcholine, norepinephrine, and glutamate
- Barbiturates also have effects on GABA and pentobarbital has been shown to be GABA-mimetic
- At high anesthetic doses, barbiturates have been demonstrated to inhibit the uptake of calcium at nerve endings
- Initial drug of choice for treating seizures in dogs and cats
- Effective, inexpensive, and convenient for administration
- Usual starting dosage is 2.5 mg/kg orally twice daily
 - Some dogs require 5 mg/kg orally twice a day to achieve therapeutic blood levels
- Dosage is adjusted according to seizure control, side effects, and serum concentrations
- Sedation may occur but usually disappears in the first week
- Polyphagia, polydipsia, and polyuria may be seen
- Hepatotoxicity occurs in a small number of cases, but it is less frequent than with most other anticonvulsants
- Peak concentrations of phenobarbital occur 2 to 3 hours after oral administration, and the lowest (trough) concentrations occur just before the next dose
- Steady-state concentrations in 2 weeks
 - Assess trough concentrations of phenobarbital once every 2 to 3 weeks until serum concentrations are in the therapeutic range of 15 to 45 µg/ml is ideal for therapeutic drug monitoring
 - Dosages as high as 10 to 20 mg/kg per day may be needed in some dogs to maintain these therapeutic blood levels
 - The response to treatment is more important than the blood level, but monitoring serum levels of phenobarbital may help to determine the cause of inadequate seizure control
- Phenobarbital is an auto-inducer of hepatic microsomal enzymes (p450 system), which can progressively decrease the elimination half-life with chronic dosing
- Monitoring for evidence of hepatotoxicity or other side effects is strongly encouraged
 - Routine blood counts and serum chemistries are usually recommended at 6-month intervals; however, a report on monitoring of human epileptics indicates that this grants little benefit, except in high-risk patients
 - Hepatotoxicity occurs in a small number of dogs treated with phenobarbital
 - Direct dose-dependent hepatotoxicity vs idiosyncratic drug reaction?
 - Dogs with serum concentrations above the therapeutic range (>45 µg/ml) are at greatest risk
- Induction of hepatic enzyme production in the absence of liver failure

- ALP (increased), ALT (high normal RR), GGT (may be transiently affected)
 - AST, BA and TBili not affected
 - Moderate hepatomegaly may be detected on AxR
 - Hepatic ultrasonography is usually normal
 - Hepatic enzymes return to normal within 6 to 8 weeks following discontinuation of phenobarbital
 - Neutropenia and thrombocytopenia have been reported in dogs
 - Immune-mediated reaction directed at cells in circulation rather than suppression of hematopoiesis in the bone marrow?
 - Long-term use phenobarbital treatment alters the thyroid axis of normal and epileptic dogs
 - Decreased T4 and fT4
 - In humans, use alters adrenal axis though this is not seen in dogs
- Potassium bromide
 - Anti-seizure activity is thought to be the result of its generalized depressant effects on neuronal excitability and activity
 - Bromide ions compete with chloride transport across cell membranes resulting in membrane hyperpolarization, thereby raising seizure threshold and limiting the spread of epileptic discharges
 - The therapeutic range is not far from the level that produces toxic side effects, such as skin eruptions, sedation, and weakness
 - Rarely seen in animals, despite the increased use of KBr
 - The initial dosage of KBr is 20 to 40 mg/kg per day
 - KBr is slow to reach steady state and has a long half-life
 - Higher levels of chloride in the diet, especially one that promotes urolith dissolution, increase the rate of renal excretion of bromide
 - Two to 3 weeks are required to reach therapeutic levels
 - Steady state is reached in about 4 months
 - The time to reach steady-state concentrations can be decreased by giving loading doses
 - Loading dose ranges from 450 to 600 mg/kg for a target serum level of 1.0 to 1.5 mg/ml
 - Loading dose is divided into equal doses given once a day for 5 days
 - Day 6: serum bromide levels are measured and if < 1mg/mL smaller loading doses can be continued for 5 days...then assess drug levels again
 - KBr levels in the serum should be determined 30 and 120 days after initiating therapy
 - Therapeutic trough concentrations are 0.8 to 3.0 mg/ml (880 to 3000 µg/ml)
- Primidone
 - Only drug specifically approved for epilepsy in dogs in the United States
 - Largely metabolized to phenobarbital and a small portion is metabolized to phenylethylmalonamide (PEMA)
 - Little or no advantage over phenobarbital, and hepatotoxicity is more frequent

- Side effects include depression, polydipsia, polyphagia, and hepatic necrosis
 - May be dramatic, but they are usually transient
- Treatment can be monitored by plasma concentrations of phenobarbital
- Phenytoin (don't waste memory space on)
 - Anticonvulsant actions are thought to be caused by the promotion of sodium efflux from neurons, thereby inhibiting the spread of seizure activity in the motor cortex
 - Believed that excessive stimulation or environmental changes can alter the sodium gradient, which may lower the threshold for seizure spread
 - Hydantoins tend to stabilize this threshold and limit seizure propagation from epileptogenic foci
 - Frequently used in humans, but its use in animals is limited because of studies showing marked species differences in the metabolism of the drug
 - Pharmacokinetics vary, depending on the route of administration, pretreatment, and treatment with other drugs
 - The action of the drug also differs among individuals, even of the same breed
- Gabapentin
 - Enhances sodium channel inactivation, enhances GABA activity, and reduces glutamate-mediated excitation
 - Dosage of 30 to 60 mg/kg every 8 to 12 hours is suggested for generalized and partial seizures. Sedation is the primary side effect.
- Topiramate/ felbamate
 - Enhances sodium channel inactivation, enhances GABA activity, and reduces glutamate-mediated excitation
 - Used as an add-on drug for generalized and partial seizures
 - T: Gastrointestinal upsets and irritability are the primary side effects
 - F: Blood dyscrasias and liver disease are potential side effects
- Zonisamide
 - Primarily reduces current through calcium channel
 - Sedation, ataxia, and anorexia are potential side effects
 - The therapeutic target range for zonisamide of 10–40 mcg/mL in people can be used as guidance regarding effective concentrations that can be targeted in dogs
 - Serum zonisamide concentration should be monitored 1–2 weeks after treatment initiation or dosage adjustment and any time seizure frequency increases
 - Currently, there are no recommendations on optimal timing of blood sampling for zonisamide concentration monitoring
- Levetiracetam
 - Enhances GABA inhibition and is used as an add-on drug for generalized and partial seizures
 - Serum concentrations are not routinely measured in clinical practice
 - Wide therapeutic index and lack of an established relationship between concentrations and both treatment response and adverse effects in people and dogs

- In people, the generally accepted range is 12–46mcg/mL
- A reference range for levetiracetam has not been established in dogs, although the range in humans often is extrapolated for use in dogs
- Imepitoin
 - Approved in Europe for treatment of idiopathic epilepsy only in dogs in 2013, in Australia in 2015 and is currently unavailable in the United States
 - Novel and selective mechanism of action that potentiates GABAergic inhibition by acting as a low-affinity, low-efficacy partial agonist at the benzodiazepine site of the GABA-A receptor, although it differs in chemical structure from benzodiazepines
- Alternative Nonpharmacologic Treatments
 - Vagal Nerve Stimulation
 - Surgical implantation of a pacemaker-like device that delivers repetitive electrical stimulation to the left cervical vagus nerve
 - Approved for use in people of all ages and seizure types
 - Mechanism by which VNS exerts its antiepileptic effect is not completely understood, but it is believed that stimulation of afferent vagal fibers influences brain activity by modulation of noradrenergic and cholinergic synaptic transmission in people and dogs
 - Approximately, half of humans treated with VNS will experience a positive response, with a >50% decrease in seizure frequency with a positive correlation with efficacy with duration of treatment
 - Dietary Alteration Treatment
 - The most well-known dietary treatment for human epilepsy is the ketogenic diet, which is a high fat, low protein, low carbohydrate diet designed to mimic the biochemical changes of fasting to potentiate mitochondrial-dependent energy metabolism in neurons and inhibition of glutamatergic metabolic pathways and synaptic transmission
 - Acupuncture
 - A recent evidence-based assessment of published randomized controlled trials concluded that the current available information does not support the use of acupuncture in the treatment of epilepsy in people
 - Homeopathy
 - Homeopathic remedies most frequently used in humans with epilepsy include silicea, cuprum, causticum, hyosciamus, Aethus cynapium, Agaricus muscaricus, Absinthium, Artemisia absinthium, Stramonium, and Cicuta virosa
 - Evidence to support the use of these treatments currently is lacking

Seizures following head trauma in dogs: 259 cases (1999–2009)

Steven G. Friedenberg, MBA, DVM; Amy L. Butler, DVM, MS, DACVECC; Lai Wei, PhD;
Sarah A. Moore, DVM, DACVIM; Edward S. Cooper, VMD, MS, DACVECC

Objective—To determine whether dogs with head trauma have a greater incidence of seizures than the general canine patient population.

Design—Retrospective case series. **Animals**—259 client-owned dogs.

Procedures—Medical records of dogs evaluated for head trauma at OSU from 1999 to 2009 were reviewed. Data were collected regarding the cause of the head trauma, physical examination and neurologic examination findings, comorbidities, and the development of seizures during hospitalization. A telephone survey was conducted to question owners regarding the development of seizures after discharge. Relationships between the nature of the head trauma and the development of seizures were then examined.

Results—3.5% of dogs with head trauma developed in-hospital seizures, and 6.8% of dogs with head trauma for which follow-up information was available developed seizures after hospital discharge, compared with an epilepsy rate of 1.4% in our hospital. Dogs that developed in-hospital seizures were significantly more likely to have been hit by a car or experienced acceleration-deceleration injury. Additionally, 10% of dogs with traumatic brain injury had in-hospital seizures. No visit or patient characteristics were significantly associated with the development of out-of-hospital seizures.

Conclusions and Clinical Relevance—Dogs with head trauma may develop seizures at a greater rate than dogs in the general canine patient population. Particularly in the immediate to early posttraumatic period, clinicians should remain vigilant for the development of post-traumatic seizures and treat patients accordingly

- In human patients, PTS are typically categorized into immediate (< 24 hours after injury), early (< 7 days after injury), and late (> 8 days after injury) onset.
- Both immediate and early seizures are considered to be direct reactions to brain damage, whereas late seizures are believed to occur as a result of secondary effects such as bleeding, cortical scarring, and reperfusion injury.
- We found the rate of out-of-hospital (late) seizures in the dogs of the present study to be greater than the rate of in-hospital (early) seizures (6.8% vs 3.5%).
- 90% of late-onset seizures in humans occur by 18 to 24 months following TBI and that human patients with late-onset PTS generally have severe neurologic impairment on examination
- In contrast, only 1 of the 5 patients in our study with late PTS had seizures within this time frame, and the patients we reported with late PTS had either absent or mild neurologic signs on examination.
- Current guidelines for human patients recommend intervention for early PTS with antiepileptic drugs for at least 1 week.
- No consensus currently exists among human neurologists regarding PTS prophylaxis.

- A recent review of both observational and prospective studies examining the usefulness of prophylactic antiepileptic drugs in humans described only mixed benefits.
- Current guidelines recommend the use of diazepam for active seizure control and phenobarbital for further seizure prevention

Prevalence of seizures in cats after head trauma

Kristina S. Grohmann, DVM; Martin J. Schmidt, Dr med vet;
Andreas Moritz, Dr med vet; Martin Kramer, Dr med vet

Objective—To determine the prevalence of seizures in cats after head trauma.

Design—Retrospective cross-sectional study.

Animals—52 cats with head trauma.

Procedures—Information was obtained from medical records of cats with head trauma and via telephone interviews of owners at least 2 years after cats had head trauma. Severity of head trauma in cats was classified with the modified Glasgow coma scale (mGCS), and the association between scores and development of seizures was determined.

Results—9 cats had moderate head trauma (mGCS score, 9 to 14), and 43 cats had mild head trauma (mGCS score, 15 to 18). None of the cats developed seizures during the follow-up period (2-9 years after head injury). The calculated 95% confidence interval for prevalence of seizures in cats after head injury was 0% to 5.6%. There was no significant relationship between severity of head trauma and the risk of seizures in cats.

Conclusions and Clinical Relevance—Results indicated the probability that cats with mild to moderate head trauma would develop posttraumatic seizures was low. However, clinicians should monitor cats with a history of head trauma for development of secondary epilepsy.

- The minimum hospitalization time for the cats was 7 days.

-During telephone interviews (from 2 to 9 years after cats had head trauma), owners reported that all 52 cats had recovered uneventfully.

-Neurologic signs or other clinical signs attributable to head trauma had not been observed in any of the cats after discharge from the clinic.