98 Chapter 98 Seizures and Status Epilepticus

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98.1 KEY POINTS

- Epilepsy refers to recurrent seizures of any type resulting from an intracranial cause and may be subdivided into true epilepsy (inherited, acquired, and idiopathic) and symptomatic epilepsy.
- Seizures are classified as partial or generalized; generalized seizures are the most common.
- Status epilepticus (SE) is a life-threatening neurologic emergency, and a common initial complaint at the emergency hospital.
- SE may cause serious systemic problems such as hypoxia, hyperthermia, systemic lactic acidosis, shock, and acute renal failure.
- Disorders that induce seizures and SE are either extracranial or intracranial.
- A complete history, physical examination, neurologic examination, and minimum database should be done in all animals with a seizure disorder.
- Further investigation of intracranial diseases using electroencephalography, magnetic resonance imaging, or computed tomography imaging, cerebrospinal fluid analysis, serology, and biopsy may be indicated.
- Seizure management is based on control of seizures by selection and appropriate administration of an anticonvulsant drug. When an underlying disease is present, it should be treated concurrently. Seizures associated with SE should be stopped as quickly as possible.

98.2 INTRODUCTION

The epidemiology of seizures in cats and dogs is unknown, despite reports of the rate,[1] prevalence,[2] and incidence.[3] Population-based animal studies are difficult to execute, thus most studies are based on data from groups of veterinary hospitals or referral-based veterinary teaching hospitals.[2] The epidemiology of seizures in groups of purebred dogs or colonies of research dogs[1] with epilepsy has been reported. For example, one population-based study reported the lifetime prevalence of epilepsy in the Danish Labrador as 3.1% (95% confidence interval 1.6% to 4.6%).[4] Although these studies are interesting, the information cannot be extrapolated beyond the research colony, hospital, or specific purebred dog geographic setting.

Despite the lack of prevalence or incidence data, it is accepted that seizure disorders are common in dogs and cats and that seizures occur more frequently in dogs than in cats. Estimates of lifetime seizure frequencies are 0.5% to 5.7% in dogs and 0.5% to 1.0% in cats.[5]

Status epilepticus (SE) is a life-threatening neurologic emergency and a common presenting complaint at an emergency hospital. Although the population prevalence of SE is not known, in one report the prevalence of SE and cluster seizures in dogs was 0.44% of all hospital admissions.[6]

Although many different types of seizures occur in dogs and cats, a classification system that is accepted universally by veterinary neurologists has not been established.[7-9] To effectively diagnose and treat dogs and cats with seizure disorders, including SE, it is important to understand the terminology, pathophysiology, and causes of seizures.

98.2.1 Definitions

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.[5]

Cluster seizures are two or more seizures within a 24-hour period.[6]

Epilepsy is recurrent seizures of any type resulting from an intracranial cause.[5]

1 *True epilepsy* originates from a nonprogressive intracranial disorder.[5]

A Inherited epilepsy is caused by a genetically determined intracranial disorder.[5]

B Acquired epilepsy is caused by a previously active intracranial disorder that is no longer active.[5]

C Idiopathic epilepsy is a seizure disorder in which the cause and mechanism for the seizures is unknown.[5]

2 *Symptomatic epilepsy* is caused by progressive intracranial disease.

Status epilepticus is a neurologic emergency requiring immediate therapy. A universally accepted definition for SE in humans or animals does not exist.[6,10] The authors recommend the definition, “continuous seizures, or two or more discrete seizures between which there is incomplete recovery of consciousness, lasting at least 5 minutes.”[11]

98.3 CLASSIFICATION

Seizures in dogs and cats may be classified as partial or generalized, based on clinical observations rather than EEG characteristics. Partial seizures originate from a focus in one cerebral hemisphere and usually manifest localized clinical signs. Partial seizures usually have an acquired cause and may be subdivided into simple partial seizures or complex partial seizures. In simple partial seizures there is 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). Additional clinical signs (e.g., autonomic signs) may be present during a simple partial seizure. Complex partial seizures are accompanied by an alteration in consciousness. There may be involuntary or compulsive actions such as chewing, licking, and defensive or aggressive behavior. Complex partial seizures have been referred to as psychomotor seizures. Both types of partial seizures may spread throughout the brain, causing generalized seizures.[5]

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Generalized seizures are the most commonly recognized seizures in dogs and cats. The most common type is the tonic-clonic seizure. Other types of generalized seizures such as tonic, clonic, or myoclonic seizures are recognized. In tonic-clonic seizures, animals lose consciousness. In the tonic phase, increased muscle tone results in limb and head extension, causing the animal to fall to the side. In the clonic phase, alternating extension and flexion of the limbs, and exaggerated chewing movements, occur. The animal usually urinates, defecates, and salivates.[5]

98.4 PATHOPHYSIOLOGY

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, including fatigue, fever, estrus, photic stimulation.

Experimentally, repeated stimulation of the rat cerebral cortex by a subconvulsive electrical stimulus caused generalized seizures over time. This phenomenon is referred to as *kindling*. [12] Following establishment of a focal seizure focus, abnormal electrical activity may be recorded over the contralateral cerebral cortex. This secondary seizure focus is termed a *mirror focus*. [13] Either the primary or secondary focus, or both, may cause seizures. The mirror focus may cause seizures even if the primary seizure focus is removed.[14] Although kindling and mirror foci are observed as experimental phenomena, they may be clinically relevant in the therapy of animals with seizure disorders.

In SE, there is failure of the normal brain homeostasis mechanisms that work to stop seizures. Proposed mechanisms for the development of SE include persistent neuronal excitation, inadequate neuronal inhibition, or both.[11] Extrasynaptic factors may be important in spreading and maintaining the seizure. An excess of excitatory neurotransmitters such as glutamate, aspartate, or acetylcholine, or antagonists of γ-aminobutyric acid (GABA) (an inhibitory neurotransmitter) may cause SE.

SE lasting 30 to 45 minutes results in brain injury in experimental animals.[15] However, brain injury probably occurs in clinical patients after a much shorter time. SE may cause neuronal necrosis, particularly in brain regions with high metabolic rates. In one report, neuronal necrosis was most severe in rats that were hypoxemic or exhibited tonic-clonic seizures.[16]

In early SE, an increase in cerebral blood flow may be protective for the brain. In late SE, cerebral blood flow decreases simultaneously as blood pressure decreases, and cerebral metabolic rate (e.g., glucose and oxygen utilization) increases. This leads to adenosine triphosphate depletion and lactate accumulation, which contribute to 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.

98.5 ETIOLOGY

Disorders that induce seizures and SE arise either outside the nervous system (extracranial) or within the nervous system (intracranial). Extracranial causes may be divided into those that originate outside the body (e.g., toxins) and those that originate within the body but outside the nervous system (e.g., liver disease). Intracranial causes of seizures are divided into progressive and nonprogressive diseases.[5]

Extracranial causes may result in generalized seizures, because they affect the brain globally. Causes of progressive intracranial disease include 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 causes of seizures include inherited, acquired, and idiopathic epilepsy. Dogs with inherited epilepsy usually are 6 months to 5 years of age. Many breeds are known or suspected to have inherited epilepsy.[17] In idiopathic epilepsy, seizures are caused by a functional problem of the brain and therefore are generalized and symmetrical.

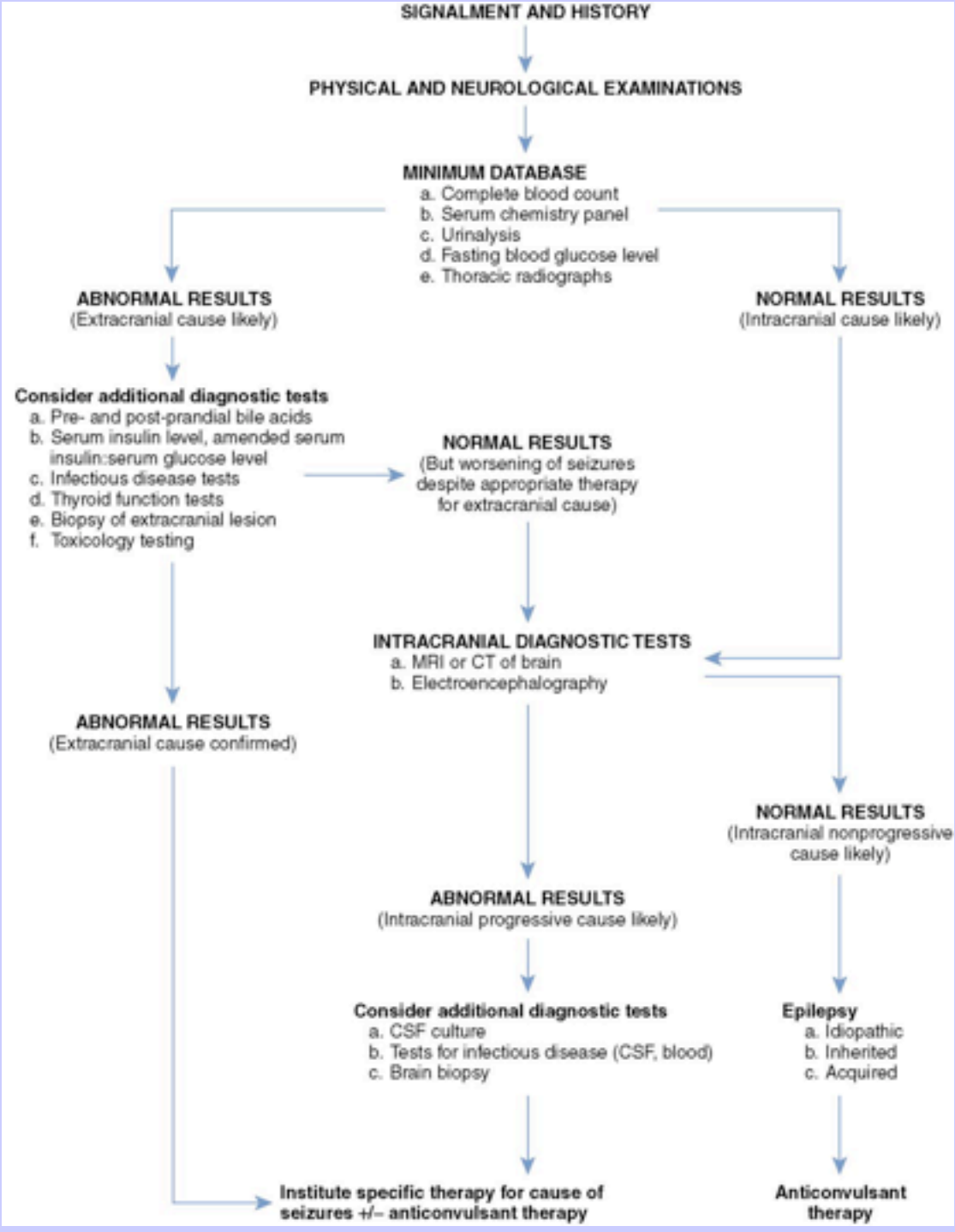
Very few veterinary studies have evaluated the clinical features of SE; therefore it is not possible to make generalizations concerning underlying causes or concerning short-term and long-term outcomes. One study[18] evaluated a cohort of 50 dogs with SE. Of those, 28% had idiopathic epilepsy, 32% had symptomatic epilepsy, and 12% had seizures secondary to a systemic insult or to physiologic stress. Forty-four percent of the dogs had not had SE previously. Many dogs were euthanized, and thus a mortality rate was not reported.[18] In another study[19] of SE in dogs with idiopathic epilepsy, 59% of the dogs had one or more episodes of SE. Survival time was shorter in dogs with both idiopathic epilepsy and SE than in those with idiopathic epilepsy alone.[19] In another study of SE or cluster seizures in dogs, a poor outcome was reported in dogs with granulomatous meningoencephalitis, poor seizure control after 6 hours of hospitalization, or SE manifest by partial seizures. Fifty-nine percent of the dogs in this study died or were euthanized.[6]

It is essential to distinguish between extracranial and intracranial (progressive and nonprogressive) diseases that cause seizures. Therapy for extracranial and progressive intracranial diseases requires not only control of seizures, but also therapy for the underlying disease.

98.6 DIAGNOSTIC PLAN

A seizure disorder is essentially a manifestation of an underlying disease; therapy is most effective when the underlying disease is diagnosed and treated. Therefore an accurate diagnosis should be established in a timely manner. In some animals an underlying cause may not be identified, as with idiopathic epilepsy. A complete history, physical examination, and neurologic examination should be done in all animals with a seizure disorder (Figure 98-1).

Figure 98-1 Diagnostic approach to seizure disorders in dogs and cats. *CSF,* Cerebrospinal fluid; *CT,* computed tomography; *MRI,* magnetic resonance imaging.



98.6.1 History

A complete general history should be obtained from the owner, as well as a specific seizure history: age at onset, frequency, and description of seizures, behavior between seizures, and temporal associations (e.g., associated with eating or not eating). A videotape of a seizure may be useful, particularly if the owner's description is insufficient.

98.6.2 Age and Breed

The age at onset is necessary to determine the most likely cause of a seizure disorder. Dogs 5 years and older usually have an acquired seizure disorder, such as a primary brain tumor. The breed is important, because inherited epilepsy is reported in certain breeds such as Beagles, German Shepherds, Poodles, and others.[17] Some breeds may have a higher prevalence of intracranial tumors (Boxers) or inflammatory disease (Maltese dogs).

98.6.3 Physical Examination

A complete physical examination should be done in all animals with seizures, to diagnose systemic problems or local problems (e.g., skull mass) that may affect the brain.

98.6.4 Neurologic Examination

A complete neurologic examination should be done in all animals with seizures. In animals with inherited or idiopathic epilepsy, neurologic examination findings between seizures most often are normal. Dogs and cats with extracranial or progressive intracranial disease may have neurologic abnormalities between seizures.

Animals may be abnormal neurologically for days after a seizure. Therefore multiple, serial neurologic examinations may be necessary in some animals after a seizure, before neurologic deficits are attributed to extracranial or progressive intracranial disease.

98.6.5 Minimum Database

A minimum database (complete blood count, serum chemistry panel, 24-hour fasting blood glucose, urinalysis) should be done on admission in all animals with seizures. In some animals, serum triglycerides and preprandial and postprandial bile acid levels should be obtained to evaluate the possibility of a portosystemic shunt and hypertriglyceridemia. If systemic disease or intracranial disease is suspected, thoracic radiography and abdominal ultrasonography should be performed to further screen for neoplastic and infectious disease.

98.6.6 Diagnostic Tests for Intracranial Disease

Further investigation of intracranial diseases, including electroencephalography (EEG), MRI, CT, CSF analysis, biopsy (for cytology, histopathology, or both), and serology, may be indicated after a minimum database is completed.

EEG is useful in some animals. When a seizure disorder is suspected, abnormal EEG findings may help to distinguish the presence of seizures from other paroxysmal nonseizure events. EEG may help the clinician to

evaluate anticonvulsant therapy, particularly in a patient undergoing treatment for SE, because the external manifestations of seizures may be abolished by drugs.[20] In the future, EEG may be useful in the classification of canine and feline seizure disorders.

MRI is preferred over CT imaging, unless acute head trauma or an acute intracranial hemorrhage is suspected. MRI and CT imaging are noninvasive, and probably yield the most diagnostic information with respect to location and extent of disease in animals with progressive intracranial problems. The results of advanced imaging may help to define a cause of the seizure disorder.

Ideally CSF is collected after MRI or CT imaging has been done. Usually CSF is collected from the cisterna magna (see Chapter 105, Cerebrospinal Fluid Sampling). Because there is risk to the patient undergoing CSF puncture, CSF is not collected in all animals with intracranial disease (see Chapter 100, Intracranial Hypertension). Usually CSF analysis results are supportive of a diagnosis, rather than providing a definitive diagnosis. However, CSF occasionally provides diagnostic information with some infections (e.g., *Cryptococcus neoformans,* bacteria), and with some neoplasms (e.g., lymphoma), and is therefore an essential part of an intracranial workup in most animals.

98.7 TREATMENT PLAN

Regardless of the underlying cause, seizure control is based on selection and administration of an appropriate anticonvulsant drug. Underlying disease, if present, should be treated concurrently. Adverse effects may limit the usefulness of an anticonvulsant drug; therefore knowledge of the mechanisms of action and drug interactions are essential. Selection of an anticonvulsant drug should be based on results of pharmacokinetic studies in the species in which the drug is intended to be used.

The ultimate goal of anticonvulsant therapy is to eradicate all seizure activity; however, this goal rarely is achieved. A more realistic goal is to reduce the severity, frequency, and duration of seizures to a level that is acceptable to the owner, without intolerable or unacceptable adverse effects on the animal. A very general guideline is to consider anticonvulsant drug therapy when the seizure frequency is greater than once every 6 weeks.

Immediate, short-term (acute) anticonvulsant therapy is required to manage SE, cluster seizures, and seizures resulting from some toxicities. Chronic (or maintenance) anticonvulsant therapy is used to manage epilepsy. Seizure control with anticonvulsant drugs is most effective when started early in the course of a seizure disorder, because each seizure may increase the probability of additional seizures secondary to effects such as kindling and mirror focus development.

98.7.1 Status Epilepticus

In SE, the goal of therapy is to stop the seizure as soon as possible. In veterinary medicine, EEG monitoring is not routine in the intensive care unit, so effectiveness of SE therapy is evaluated by the cessation of the outward physical manifestations of a seizure. Therefore, in some animals, although there are no obvious clinical signs of SE, the brain may still have ongoing seizure activity that may negatively affect outcome. As with many disorders in veterinary medicine, there are no controlled clinical trials that may be used to guide therapy. Therefore recommended treatments are guidelines only (Table 98-1).

Treatment should be divided into the (1) immediate emergency evaluation and treatment (such as airway, breathing, cardiovascular function, body temperature, glucose concentration, and blood pressure) (see Chapter 2, Patient Triage) and (2) pharmacologic treatment (see Table 98-1). Animals that are admitted in SE or with

cluster seizures, may have cerebral edema, and mannitol administration should be considered (see Chapter 100, Intracranial Hypertension).

98.7.2 Pharmacologic Therapy for Status Epilepticus

98.7.2.1 Benzodiazepines

Diazepam is the first-line agent of treatment of dogs and cats with SE. It is lipid soluble and enters the brain rapidly when given intravenously, intranasally, or per rectum. It binds to the GABA receptor and enhances neuronal hyperpolarization, reducing neuronal firing. The duration of action is short, so a maintenance anticonvulsant (such as phenobarbital) should be administered concurrently, to avoid recurrence of seizures or SE when diazepam levels in the brain decrease. For animals not currently receiving phenobarbital, a loading dosage is administered. Owners may administer PR diazepam to their animals. Midazolam is a water-soluble benzodiazepine and may be used to manage SE. Although the IV route is preferred, midazolam may be given IM if IV access cannot be obtained.

Table 98-1 Anticonvulsant Drugs for Status Epilepticus in Dog and Cats

Drug	Dosage	Comments
Diazepam (first-line)	*IV bolus:* 0.5 to 1 mg/kg may be repeated 2 to 3 times *CRI:* 0.5 to 1 mg/kg/hr *Per rectum:* 0.5 to 1 mg/kg (2 mg/kg if receiving concurrent phenobarbital)	IV injections and infusions should be administered into a central vein
Phenobarbital (maintenance anticonvulsant: use concurrently with diazepam)	2 to 4 mg/kg IV q20-30 min to a total of 18 to 20 mg/kg	Administer concurrently with diazepam to prevent recurrence of seizures once diazepam levels fall in the brain This dose may be repeated every 20 to 30 minutes until a cumulative dosage of 18 to 20 mg/kg has been given Once seizures are controlled a maintenance dosage of phenobarbital is used (3 to 5 mg/kg IV or IM q12h for 24 to 48 hours). Oral anticonvulsant therapy should be resumed or initiated every 12 hours as soon as the animal is able to swallow
Pentobarbital (second-line)	6 to 15 mg/kg IV slow bolus, followed by a CRI of 0.5 to 2 mg/kg/hr to effect	Strict monitoring of physiologic parameters is required
Propofol (third-line)	2 to 8 mg/kg slow IV bolus, given as 25% of the total dose every 30 seconds until desired effect achieved	CRI should be considered (0.1 to 0.4 mg/kg/min) Strict monitoring of physiologic parameters is required (may stop overt manifestations of seizures, but may not stop seizure activity)

CRI, Constant rate infusion; *IM,* intramuscular; *IV,* intravenous.

If SE continues or further seizures occur, additional boluses of diazepam may be given, or a constant rate infusion (CRI) of diazepam may be used. If the SE does not stop, or recurs multiple times, then barbiturates (pentobarbital) are used. The dosage of phenobarbital should be reviewed at this point in time, to ensure that an adequate dose has been administered.

98.7.2.2 Barbiturates

Barbiturates potentiate the action of GABA by interfering with sodium and potassium transmission in the neuronal membrane. Because the half-life of most drugs used to manage SE is short, a maintenance anticonvulsant *must* be part of the treatment regimen. Phenobarbital is the most commonly used maintenance anticonvulsant in dogs with SE because it can be given intravenously.

Pentobarbital is used as a second-line drug if benzodiazepines fail, but it has a limited anticonvulsant effect. Pentobarbital is administered as a bolus, followed by a CRI. Pentobarbital may cause sedation, respiratory depression, hypotension, and death. Animals that are heavily sedated or anesthetized should be intubated so that an open airway is maintained. Other physiologic parameters (such as heart rate, blood pressure, oxygenation, etc.) should be monitored regularly or continuously. Therefore the dosage should be titrated carefully to stop or reduce the motor activity from the seizure, but to avoid anesthesia if possible. During recovery, it may be difficult to determine if the animal is recovering from the pentobarbital or is still having seizures.

98.7.2.3 Propofol

Propofol is a rapid-acting, lipid soluble general anesthetic agent. It is a third-line drug for the management of SE in dogs and cats. The anticonvulsant effect of propofol is likely due to its GABA agonist activity.[21] There are case series describing its use in animals and humans with SE.[21,22] However, propofol use is controversial, because seizures have been associated with its use in humans[23] and in a dog.[24] In one study, humans with SE who were treated with propofol had a higher mortality rate than those treated with midazolam.[22]

98.7.3 Chronic Seizure Disorders

Successful anticonvulsant therapy depends on the maintenance of plasma concentrations of appropriate anticonvulsant drugs within a therapeutic range defined for the species in which the drug is to be administered. Therefore anticonvulsant drugs that are eliminated slowly should be employed. The elimination half-life of anticonvulsant drugs varies considerably between species. Few anticonvulsant drugs used in humans are suitable for use in dogs and cats, largely due to species differences in pharmacokinetics. Pharmacokinetic data for and clinical experience with many anticonvulsant drugs are lacking in cats. Selection should be based on the known pharmacokinetic properties of a drug in the species in which it is to be administered (see Chapter 186, Anticonvulsants).

Phenobarbital and bromide are the first-line of anticonvulsant drugs recommended for chronic seizure disorders in dogs. Phenobarbital is the first-line anticonvulsant in cats.

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98.8 SUGGESTED FURTHER READING*

SW Bateman, JM Parent: Clinical findings, treatment, and outcome of dogs with status epilepticus or cluster seizures: 156 cases (1990-1995). *J Am Vet Med Assoc*. **215**, 1999, 1463, *One of the few retrospective studies on SE and cluster seizures in dogs. Patient outcome discussed.*

RA LeCouteur, G Child: Clinical management of epilepsy of dogs and cats. *Probl Vet Med*. **1**, 1989, 578, *A thorough, well written review discussing clinically important aspects of epilepsy in dogs and cats*.

MD Lorenz, JN Kornegay: Seizures, narcolepsy and cataplexy. In MD Lorenz, JN Kornegay (Eds.): *Handbook of veterinary neurology*. ed 4, 2004, Saunders, St Louis, *Clinically useful chapter that includes many relevant tables (such as breeds with primary generalized epilepsy)*.

* See the CD-ROM for a complete list of references